Australian Government
Department of Health
Office of the Gene Technology Regulator

Technical Review of the Gene Technology Regulations 2001

Decision Regulation Impact Statement

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Contacts

Office of the Gene Technology Regulator
MDP 54
GPO Box 9848
Canberra ACT 2601 Australia

Telephone: 1800 181 030
Fax: (02) 6271 4202
Email: ogtr@health.gov.au
Website: www.ogtr.gov.au

Executive summary

Significant scientific advances have occurred in the field of gene technology since the Gene Technology Regulator (the Regulator) completed the last technical review of the Gene Technology Regulations 2001 (the GT Regulations). As a result, some areas of Australia's gene technology legislation are not providing clear and unambiguous requirements for those working with genetically modified organisms (GMOs).

On the whole, the GT Regulations are working well with no major changes to their overall operation proposed at this time. However feedback received from stakeholders as part of the *Technical Review of the Gene Technology Regulations 2001* (the Technical Review), as well as operational experience from within the Office of the Gene Technology Regulator (OGTR), have demonstrated a need to address specific technical issues within the legislation.

The objective of the Technical Review is to keep the GT Regulations up to date with advances in technology and increased scientific understanding. The Technical Review is limited to the existing policy settings of the regulatory scheme, and cannot extend to topics outside of the current scope of the GT Regulations, for example, the safety assessment and labelling of genetically modified food.

The recommended amendments were developed following consultation on a discussion paper in late 2016, and finalised following further consultation in late 2017-early 2018. Consideration was given to issues raised in submissions, OGTR's experience, current scientific understanding, potential risks, regulatory burden implications for stakeholders, whether regulatory burden would be commensurate with risks, and the policy intent of the *Gene Technology Act 2000* and scheme.

A Consultation Regulation Impact Statement (OBPR Reference 22513), consistent with Council of Australian Governments' best practice regulation requirements, and draft amendment proposals were the subject of public consultation from 30 November 2017 to 21 February 2018. Three options were presented:

- Option 1 – retain the current GT Regulations
- Option 2 – amend the GT Regulations by introducing all elements of the draft amendments
- Option 3 – amend the GT Regulations by introducing some, but not all, of the amendment elements from Option 2.

The Regulator concludes that implementing the full suite of recommended amendments to the GT Regulations, as finalised following consultation, will have the greatest net benefit at this time within the constraints of this Technical Review for the following reasons:

- the amendments are commensurate with risk, and impose regulatory burden only when needed to protect human health and safety and the environment from risks posed by or as a result of gene technology
- research and industry sectors would benefit from the legal clarity gained by implementing the recommended amendments
- the amendments are anticipated to lead to only a minor increase in regulatory burden costs to regulated stakeholders, from transitional costs and the

proposal to increase regulatory oversight of contained dealings with gene drive GMOs.

The Technical Review has progressed in parallel to the Third Review of the Gene Technology Scheme (the Scheme Review), being undertaken for the Legislative and Governance Forum on Gene Technology. The Scheme Review has also considered issues arising due to technological developments, and further policy work in this area is likely. Amendments to the GT Regulations recommended through the Technical Review are considered an interim approach to provide stakeholders and the Regulator with clarity and certainty while the work anticipated to flow from the Scheme Review progresses.

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Introduction

The recommended amendments to the Gene Technology Regulations (the GT Regulations) are being presented to the Legislative and Governance Forum on Gene Technology (LGFGT) for agreement as the final stage of an extensive process undertaken by Gene Technology Regulator (the Regulator) as part of the *Technical Review of the Gene Technology Regulations 2001* (the Technical Review).

All dealings with genetically modified organisms (GMOs) must be conducted in accordance with the Commonwealth's *Gene Technology Act 2000* (the GT Act), the GT Regulations and, where applicable, corresponding State/Territory legislation. As such it is necessary to ensure that each piece of legislation remains up to date and fit for purpose.

The Technical Review of the GT Regulations (initiated by the Regulator) aims to provide clarity about whether organisms developed using a range of new technologies are subject to regulation as GMOs and ensure that new technologies are regulated in a manner commensurate with the risks they pose.

What is a Regulation Impact Statement (RIS)

If regulatory change is being considered, the regulatory impact of options for change must be assessed. The Council of Australian Governments (COAG) process for preparing and submitting a RIS comprises two stages. The first stage involves consultation on the costs and benefits of the proposed changes; this is known as the Consultation RIS. The second stage involves preparation of a recommendation report, or Decision RIS, that includes an analysis of comments on the Consultation RIS, as well as evidence on the costs and benefits of the proposed changes.

This Decision RIS has been prepared in accordance with COAG best practice regulation requirements, and includes the following sections:

- a statement of the problem (section 1)
- a statement of the possible options to address the problem (section 2)
- an impact analysis of the options, including an evaluation of the preferred option (section 3)
- details of the consultation undertaken (section 4) and
- further information about implementation and review (section 5).

Current Gene Technology Regulations 2001

Australia's national regulatory scheme for gene technology is comprised of the Commonwealth GT Act and GT Regulations, and corresponding State and Territory laws. The Commonwealth GT legislation took effect on 21 June 2001.

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."

Australia's gene technology regulatory scheme was set up in 2000 in response to a growing community view that GMOs posed 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[1].

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.

Amendments to the GT Regulations have occurred through two technical reviews (amendments commencing 31 March 2007 and 1 September 2011), the 2005-6 statutory review of the GT Act (commencing 1 July 2007) and several other consequential amendments.

Many of the previous amendments have related to technical and operational matters that have enhanced the effectiveness of the GT scheme and assisted user compliance by making the Regulations clearer and easier to understand.

Objectives of the Technical Review: addressing technological advances

The objective of this Technical Review is to keep the GT Regulations up to date with advances in technology and increased scientific understanding, so as to address the problems detailed in Section 1. This includes providing clarity about whether organisms developed using a range of new technologies are subject to regulation as GMOs and ensuring that gene technology is regulated in a manner commensurate with the risks posed.

The Technical Review cannot alter the policy settings of Australia's gene technology regulatory scheme, meaning that the recommended changes to the GT Regulations only alter the status of organisms or techniques that do not already receive clear treatment in the legislation, or where scientific understanding of the risks they pose has changed.

Likewise, no changes are recommended that relate to topics outside of the current scope of the GT regulations, for example, regulation of genetically modified food or the application of new technologies to humans or embryos.

The recommended amendments to the GT Regulations, which are discussed in detail in Section 2 (options) have been prepared on the basis of submissions received from stakeholders and learnings from within the OGTR. The key recommended amendments cover the following topic areas:

- amendments in response to technological developments (implementing Option 3 from the October 2016 Discussion Paper and clarifying the regulatory status of some RNA interference techniques) – refer Sections 1.1, 2.1 and 3.3

[1] 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".

- amendments to keep the classification of contained dealings with GMOs up to date – refer Sections 1.2, 2.2 and 3.4, and
- amendments that clarify, but do not change, the regulatory status of certain organisms – refer sections 1.3, 2.3 and 3.5.

Concurrent review of policy settings

The Technical Review has progressed in parallel to the Third Review of the Gene Technology Scheme (the Scheme Review), being undertaken for the LGFGT. The Scheme Review has considered policy issues arising due to technological developments, and further policy work in this area is likely, particularly in light of Finding 3 of the Preliminary Report released in March 2018:

> **Finding 3**: The [Scheme] Review found that there are existing definitions in the *Gene Technology Act 2000* and Gene Technology Regulations 2001 that may not appropriately classify a range of advances in technology (for example, the definitions of 'gene technology' and 'genetically modified organism', including the use of the terms 'other genetic material' and 'foreign').
>
> In both the Australian and international context, the value of having consistent definitions is well understood, as is recognition that definitions have a primary role in the classification of technologies and subsequent regulatory requirements. Any examination of definitions should therefore take into account concurrent work, including the current Technical Review of the Gene Technology Regulations 2001, as well as ongoing work internationally.

The complex considerations necessary to fully address this finding are anticipated to take some time before implementation. Amendments to the GT Regulations recommended through the Technical Review are considered an interim approach to provide stakeholders and the Regulator with clarity and certainty while the work anticipated to flow from the Scheme Review progresses.

1. Statement of the problem

Since the last technical review of the GT Regulations, a number of issues have been identified which show that Australia's current gene technology legislation is not as effective as it could be in terms of providing clear and unambiguous regulatory requirements for those working with GMOs.

The issues identified include the following:

- **ambiguity in the GT Regulations due to technological developments** – new technologies for modifying genetic sequence and gene expression have developed rapidly and so in some cases it is not clear whether organisms modified by certain techniques are 'GMOs' or not.
- **the need to keep the categorisation of contained dealings with GMOs up to date** – the techniques and organisms used in gene technology research have changed since the GT Regulations were last reviewed, as has understanding of risk.
- **the need for improved clarity** regarding the regulatory status of organisms that are not themselves categorised as GMOs but have been derived from GMOs. There is no problem with the current regulatory status of these organisms from a risk perspective; rather, improved clarity would assist user understanding and compliance.

Should the option to amend the GT Regulations be pursued, minor administrative amendments will also be introduced in addition to the issues indicated above. These administrative matters are summarised at **Appendix A**.

In identifying these issues, the Office of the Gene Technology Regulator (OGTR) recognises that the GT Regulations are fit for purpose, and appropriately support the object of the regulatory scheme (see section 2). The Technical Review is focusing on technical aspects of the regulatory scheme, within the current policy framework.

1.1 Ambiguities in the GT Regulations due to technological developments – what is a GMO

Currently **ambiguities exist in the GT Regulations** because new technologies for altering genetic sequence and gene expression are not specifically addressed in the legislation. Under existing provisions, it is not clear whether (or not) organisms that have undergone several specific techniques are within, or excluded from, the scope of regulation under the GT Act:

- site-directed nuclease (SDN) techniques with or without a template to guide small changes (SDN-2 and SDN-1, respectively)
- oligo-directed mutagenesis (ODM) and
- some RNA interference (RNAi) techniques.

This issue has also been identified through the Scheme Review, as detailed in the Preliminary Report[2] (see discussion of Finding 3 in Introduction). Additional information on SDN techniques, ODM and RNAi is provided at **Appendix D**.

[2] Available on the Department of Health website.

Why is it a problem?

Australia's gene technology legislation does not in explicit terms address site-directed nuclease techniques, ODM or RNAi techniques. It has become apparent through interactions with regulated stakeholders that it is not clear whether organisms produced using some of these new techniques meet the definition of 'GMO' in the GT Act.

Item 1 of Schedule 1 (exclusions from the definition of 'GMO') has been a primary source of ambiguity in this area. The Schedule was established before many of the new technologies existed, and contains many undefined terms. In the absence of a clear meaning for this item, stakeholders may have interpreted it in a variety of ways, including in relation to the new technologies described above.

If organisms are GMOs, activities with them (defined as "dealings") require authorisation under the GT Act. Dealing with a GMO without appropriate authorisation is prohibited under the GT Act.

Ambiguity in the GT Regulations in these areas is therefore a problem because organisations or individuals undertaking work in this area are not able to confidently determine the regulatory requirements to which they must comply when using these new technologies.

What are the risks?

If regulatory requirements continue to be set against a baseline of legislative provisions that do not account for these technologies, there is a risk that the level of regulation may not be commensurate with risk. This could result in under-regulation, which could result in inappropriate management of risks to human health and safety and the environment, or over-regulation, which could inhibit research using these technologies.

Ambiguity in this area raises the risk that organisations or individuals will not seek the necessary approvals, mistakenly believing that such approvals are not required. If organisations or individuals undertake work with new technologies without appropriate approvals, they may be liable for breaching the GT Act and associated penalties may apply. In this scenario, necessary risk management measures may not be in place compromising the health and safety of people and the environment.

There is also a risk that ambiguity will inhibit use of the technologies, as organisations may delay their work because they are unsure about the regulatory requirements, or may not proceed with work because they mistakenly believe that there are prohibitive regulatory burdens. Possible consequences of this are that the progress of basic research may be held back, and that products (such as food crops or human or animal therapeutics) may not be commercialised. Alternatively there may be delays in bringing new products to market, meaning that the benefits from these products may not be made available in Australia. In the longer term, if uptake of these technologies continues to be inhibited this could hamper industry development and affect the international competitiveness of Australian businesses. It is also possible that the Regulator would be unable to successfully prosecute an intentional breach of the GT Act due to lack of legal clarity. The required legal arguments may be difficult to make given the absence of explicit references to the above described new technologies in the GT Regulations.

1.2 Keeping the categorisation of contained dealings with GMOs up to date

Dealings with GMOs that do not involve intentional release to the environment are categorised in the GT Regulations on the basis of risk:

- Exempt dealings, which have been assessed as posing negligible risks, and do not require approval from or notification to the Regulator
- Notifiable low risk dealings (NLRDs), which have been assessed as posing low risk provided that standard conditions are met, and must be assessed by an Institutional Biosafety Committee (IBC) and notified to the Regulator annually
- Dealings Not involving Intentional Release (DNIRs) to the environment, which must undergo case-by-case assessment by the Regulator and be carried out in accordance with tailored licence conditions.

Updating categorisations to ensure they are commensurate with risk has been a major focus of previous technical reviews of the GT Regulations, and there is again a need to update several aspects of categorisation of contained dealings.

Why is it a problem?

The need to update contained dealings classifications has come about because of ongoing scientific developments and improved understanding of risk, specifically:

- newly available technologies, for example use of CRISPR/Cas9 to make gene drive GMOs, have not been considered before
- new parent species are being used in gene technology research, and their categorisation has not been considered before
- with some categorisations becoming well established, GMO dealings posing equivalent risk should be considered for equivalent classification and
- over time, aspects of current classifications that initially were not clear enough have become apparent, e.g. dealings with viral vectors with no host.

What are the risks?

As use of technology changes or the organisms used in research change over time, the classification of contained dealings with these GMOs continues to be set by existing provisions, which were not written with the new applications in mind. As a result, classifications may set a greater level of oversight than is warranted on a risk basis, or may set an insufficient level of oversight than is required.

If contained dealings with GMOs are subject to excessive regulatory requirements, there is a risk that this part of the gene technology regulatory scheme could be seen by researchers as unnecessarily burdensome and may result in potentially valuable work with these organisms not being undertaken because of the regulatory requirements associated with them.

If contained dealings with GMOs are classified at a lower level than is appropriate for the risks they may pose, inadequate risk management measures may be applied.

This could possibly lead to harms to human health and safety and the environment being realised.

1.3 Clarifying the regulatory status of organisms derived from GMOs

OGTR stakeholders have sought clarity about the regulatory status of organisms derived from GMOs, but which have not inherited traits that occurred because of gene technology (also known as 'null segregants'), and organisms that previously were temporarily modified by gene technology but the modification (and any resulting traits) are no longer present in the organism. This demonstrates that the legislation does not provide enough clarity about these organisms.

Why is it a problem?

The current regulatory status of these organisms is commensurate with risk, and there is no proposal to make any changes to that status. However, it has become apparent from interactions with stakeholders that there are different understandings of the language used in the GT legislation to describe the regulatory status of these organisms.

What are the risks?

Some organisations or individuals are not able to determine the regulatory requirements to which they must comply when working with these organisms. Risks associated with this perceived lack of clarity are similar to those described in section 1.1, in particular, work in this area may be inhibited by uncertainty around regulatory requirements.

1.4 Can the GT Regulations address these problems?

The problems described in sections 1.1-1.3 may be addressed through amendments to the GT Regulations. For the problems described in section 1.2, the GT Regulations set the current regulatory requirements and changes to these requirements are the only effective means to address the problems.

For the problems described in sections 1.1 and 1.3, regulatory status could be clarified through amendments to the Regulations or through changes to the GT Act. However, only changes to the GT Regulations that are within current policy settings are possible through the Regulator's Technical Review.

In relation to ambiguities due to technological developments (section 1.1), findings in the Preliminary Report for the Scheme Review indicate further policy consideration is likely to be given to existing definitions in the GT Act in light of technological advancements. However, given the complexity of the underlying issues, determining how to amend the definitions and implementing legislative amendments may take some years. Amendments to the GT Regulations through the Technical Review are necessary to provide stakeholders and the Regulator clarity and legal certainty to continue operating in the interim period.

There is no other existing regulation that addresses the regulatory status of and regulatory requirements for the above described organisms and dealings.

2. Policy options under consideration

OGTR developed draft GT Regulations amendment proposals to address the three problems identified in Section 1. Through public consultation, stakeholders were asked to choose whether they did not support any amendments, or whether they supported the draft amendments proceeding in full or in part. The amendment proposals were further refined following this consultation (refer Section 4 for details of the consultations undertaken). The finalised recommended amendments and the alternative approaches put forward by submitters in relation to some topics are discussed below according to the three problems.

2.1 Addressing technological developments

The key elements of the recommended amendments to address technological developments are:

- Providing clarity about the regulatory status of organisms modified using SDN techniques and ODM: organisms modified using SDNs without templates to guide genome repair (i.e. SDN-1) would not be regulated as GMOs; organisms modified using SDN-2 and ODM would continue to be regulated as GMOs.
- Listing the application of RNA molecules to induce RNAi as a technique that is not gene technology provided several requirements are met. RNAi techniques which involve inserting sequences into the genome or use of viral vectors would continue to result in GMOs which are subject to regulation.

These and additional amendments to remove ambiguity are detailed below, and **Appendix B** cross-references all proposals to items in the recommended amendments.

2.1.1 New Technologies - SDN-1, SDN-2, ODM

Organisms modified using SDN-1 would be excluded from regulation under the recommended amendments, as organisms that are not GMOs, on the basis of risk, compliance enforceability and consideration of the policy settings of the regulatory scheme, as discussed below. If a template is used to guide genome repair (i.e. SDN-2) the resulting organisms are currently considered GMOs, as are organisms modified using ODM, and these would continue to be regulated.

In nature, DNA breaks in the genome of an organism can be caused by a range of natural factors, and cells have evolved mechanisms to scan DNA for breaks and to repair them. The same repair mechanisms are employed, regardless of the cause of the DNA break. In most cases, cells repair the DNA without any sequence changes or with small deletions only; occasionally, other sequence changes are the result. These DNA changes give rise to the genetic variability which is the foundation for biological evolution, for example preventing expression of a protein, and altering or deleting a small part of a protein. Most commonly, these types of sequence changes reduce the fitness of the organism. Natural mutations are not regulated as gene technology.

SDN-1 involves using a site-directed nuclease to cause a DNA break at a chosen DNA sequence which is then repaired using the cell's natural mechanisms. The DNA repair is no more directed than the repair of DNA breaks occurring through other

causes, resulting in the same range of possible DNA changes and the same range of possible changes to the characteristics of the organism as could occur in nature.

Site-directed nucleases are known to cause DNA breaks at sequences that do not perfectly match their intended target sequences, known as off-target effects. While there is a much current research into improving the specificity of site-directed nucleases, and many published examples of highly specific applications, there are also publications demonstrating the prevalence of off-target effects in various experimental scenarios. Importantly, the repair of off-target DNA breaks leads to the same range of DNA changes as are possible through repair of naturally occurring DNA breaks.

Because the changes brought about through SDN-1, including off-target effects, are no different to natural mutations, they do not give rise to any different risks to natural mutations. At the commencement of the gene technology regulatory scheme, the list of 'organisms that are not GMOs' in Schedule 1 of the GT Regulations was intended to exclude techniques on the basis that they "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."[3] Excluding organisms modified using SDN-1 from regulation as GMOs is consistent with this intention, and appropriate on the basis that these organisms do not pose different risks to natural mutants.

Organisms, including those that are not regulated as GMOs under the GT Act, may be subject to regulation by other agencies, depending upon their characteristics and intended uses, including:

- Organisms with pesticidal properties or that are veterinary medicines require approval from the Australian Pesticides and Veterinary Medicines Authority under the *Agricultural and Veterinary Chemicals Code Act 1994*
- Organisms that are human therapeutics require approval from the Therapeutic Goods Administration under the *Therapeutic Goods Act 1989*
- Import of organisms to Australia may require approval from the Department of Agriculture and Water Resources under the *Biosecurity Act 2015*
- Organisms that are biocontrol agents require authorisation under the *Biological Control Act 1984*, which is administered by the Department of Agriculture and Water Resources and mirrored by State and Territory laws
- Organisms that are also novel foods require pre-market safety assessment by Food Standards Australia New Zealand (FSANZ) under Standard 1.5.1 of the *Australia New Zealand Food Standards Code*
- Other organisms may require authorisation under the *Environmental Protection and Biodiversity Conservation Act 1999*, administered by the Department of Environment
- Harmful biological agents are regulated under the Security Sensitive Biological Agents Regulatory Scheme under the *National Health Security Act 2007*, administered by the Department of Health.

Sequence changes brought about by SDN-1 are detectable with prior knowledge. However, sequencing to detect those changes cannot empirically determine the method by which they were produced, and cannot distinguish SDN-1 outcomes from

[3] 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.

natural mutations. The problem of detectability undermining compliance enforcement was considered when the scheme was originally put in place, when it was concluded that "… 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)."[4] All GMOs currently licenced for commercial release in Australia can be unambiguously identified by their introduced DNA sequence. This would not be possible for organisms modified using SDN-1.

Excluding organisms modified by SDN-1 from regulation would be consistent with GMOs being defined on the basis of having been modified by the process of gene technology (also known as a process regulatory trigger). The use of a template to direct sequence changes is a hallmark of the techniques generally considered to be gene technology since inception of the regulatory scheme. Organisms modified using SDN-2 and SDN-3, which use templates to guide sequence changes, would continue to be regulated as GMOs.

The recommended amendments would list organisms modified using SDN-1 as organisms that are not GMOs. While listing SDN-1 as a technique that is not gene technology was considered, this approach was discarded because it would also exclude from regulation any intermediate GMOs produced in the course of SDN-1, for example organisms stably expressing a site-directed nuclease.

2.1.2 Item 1 Schedule 1

Repealing item 1 of Schedule 1 is recommended to improve clarity in the GT Regulations, particularly in relation to organisms modified using SDN-1, SDN-2 and ODM. The vast majority of organisms excluded from regulation under this item at the commencement of the regulatory scheme were organisms modified using mutagenesis techniques. The status of mutagenised organisms as not being GMOs was confirmed by amendments in 2006 listing chemical and radiation-induced mutagenesis as techniques that are not gene technology in Schedule 1A. As a result, the status of these organisms as not being GMOs would not change if item 1 of Schedule 1 was repealed.

OGTR is aware of two additional organisms currently excluded from regulation through item 1, NoGall and VaxSafe PM. To maintain their status, the recommended amendments would specifically list these organisms in replacement items on Schedule 1 under their strain names.

2.1.3 RNAi

RNAi techniques involving directly applying RNAs to temporarily induce RNAi, referred to below as RNA-delivered RNAi, would be listed as techniques that are not gene technology under the recommended amendments. This would result in organisms modified using these techniques not being classified as GMOs.

RNA-delivered RNAi involves gene-specific RNAs being introduced to an organism to reduce protein expression from the targeted gene until the introduced RNAs are degraded. This occurs through mechanisms that degrade the targeted RNA transcript, inhibit translation of the targeted RNA transcript into protein, and/or

[4] GT Regulations Regulation Impact Statement Section 4 part (a), discussion of having no list of organisms that are not GMOs, published as part of the 2001 Explanatory Statement.

repress transcription by methylating the targeted genomic DNA. No new proteins are made through such processes.

The effects of genomic DNA methylation can persist for variable periods after the introduced RNAs are degraded, prolonging the effect on the target gene. The introduced RNAs may also reduce expression of genes with similar sequences to the target gene. However, both of these effects are within the range of effects possible through natural mutations, which can also reduce the level of expression of existing genes or inactivate genes. Excluding RNA-delivered RNAi techniques from regulation is consistent with the original intent of exclusions to regulation from 2001, some of which were listed on the basis that they "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."[5]

To ensure that only short-lived RNAi techniques are excluded, this measure would require that the organism's genomic DNA sequence cannot be changed by the technique. This relates only to nucleotide sequence changes, and not to genomic DNA methylation. RNAi techniques resulting in heritable changes in the organism's DNA sequence, such as vector-mediated RNA delivery or stable integration of hairpin transgenes, would continue to be regulated as gene technology.

To ensure that the range of excluded techniques cannot confer novel protein functions, which warrant regulatory oversight, the measure would also require that the introduced RNA cannot be translated into a protein. Finally, the measure would not apply if production of infectious agents is possible. Only RNAi techniques are the intended scope of this exclusion, not techniques involving infectious non-coding RNAs such as viroids.

This measure is intended to apply across any method to introduce RNA, including soaking or spraying plant parts with RNA solutions, exposing cultured cells to RNA solutions, or injecting RNA into animal tissues. RNA would be considered introduced into the organism it is directly applied to, and any organisms subsequently receiving it, for example insects feeding on plant parts to which RNA has been applied. Provided the other requirements are met, the forms of RNA within the scope of this measure include short interfering RNAs, short hairpin RNAs, double stranded RNAs, and artificial microRNAs, whether or not they match an endogenous sequence.

This amendment would not impact upon or change the requirements of product regulators such as the Australian Pesticides and Veterinary Medicines Authority or the Therapeutic Goods Administration in relation to these techniques.

2.1.4 Alternative approaches to technological developments

Two alternative approaches were considered through the Discussion Paper consultation, and these continued to have the support of some submitters to the amendment proposals consultation.

More oversight of new technologies

Some submitters supported regulating organisms modified using SDN-1, SDN-2 and ODM as GMOs, on the basis that these organisms may pose risks, and the

[5] 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.

techniques are not yet well understood. Most supporters of this approach opposed listing RNA-delivered RNAi as a technique that is not gene technology, supported repealing item 1 of Schedule 1, and opposed listing NoGall and VaxSafe PM as organisms that are not GMOs.

However, as discussed above, organisms modified using SDN-1 and RNA-delivered RNAi do not warrant regulation for several reasons:

- they pose equivalent risks to organisms with natural mutations, and so regulating these organisms would not be commensurate with the risks they pose and
- 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.

Reduced oversight of new technologies

Some submitters supported excluding organisms modified using SDN-1, SDN-2 and ODM from regulation as GMOs, on the basis that these organisms, particularly plants, pose risks similar to conventionally bred organisms, which are not regulated. Supporters of this approach opposed listing organisms modified using template-guided SDN techniques and ODM as GMOs; some also opposed the repeal of Schedule 1 item 1; and some also sought to broaden the amendment that would exclude organisms modified by SDN-1 from regulation, to also exclude newer base editing techniques from regulation.

However, within the constraints of the current policy settings OGTR considers it appropriate to continue regulating organisms modified using SDN-2 and ODM for the following reasons:

- Under the current policy framework, regulatory exclusions apply equally to all plants, animals and microbes modified by particular techniques. However, excluding all organisms modified using SDN-2 and ODM from regulation may not be commensurate with risk, particularly with pests or disease-causing organisms.
- Successive rounds of modification using SDN-2 or ODM could result in substantial changes which may pose risks warranting regulatory oversight. While regulatory exclusions based upon product features could address this, such exclusions would need to be considered against the process-based definition of GMO[6] in the GT Act, which is beyond the scope of the Technical Review.

OGTR acknowledges that modifications obtained by SDN-2 and ODM can be in the same range as natural mutations, but can also extend beyond that range to potentially pose novel risks in some types of organisms. Within the current policy settings, regulating all organisms modified using SDN-2 and ODM is the only approach that would allow regulatory oversight of those organisms potentially posing novel risks.

[6] The appropriateness of the process-based definition of 'GMO' in the GT Act has been considered through Scheme Review. Finding 8 of the Preliminary Report is that "The [Scheme] Review heard strong arguments to support the maintenance of a process-based trigger as the entry point for the Scheme (i.e. a broad range of technologies, including new technologies, are within the scope of the Scheme)."

In the context of the Scheme Review, OGTR notes that a different regulatory approach that appropriately manages novel risks may be developed through reconsideration of the policy settings, particularly in relation to Finding 3 of the Preliminary Report (as discussed in Section 1.1).

Early development of a new application of CRISPR-Cas9, known as base editing, has emerged during this Technical Review. Base editing utilises DNA-modifying enzymes to directly convert nucleotides at targeted genomic sequences. Base editing differs from SDN-1 and SDN-2 in that it utilises a Cas9 variant which has no nuclease activity and requires further enzyme activity, eg cytidine deaminase or adenine deaminase. Several submitters proposed that the amendment excluding SDN-1 from regulation should be altered to also exclude base editing, on the basis that neither process requires a template to guide the resulting modification. OGTR considers there is currently insufficient knowledge about base editing applications and their possible outcomes to justify extending the amendments in this way.

2.2 Updating the categorisation of contained dealings with GMOs

The recommended approach to update the categorisation of contained dealings with GMOs and alternative approaches suggested by submitters on some topics are presented below. Submitters did not suggest alternative approaches to the majority of these proposals.

2.2.1 Gene drives

Recommended approach

Given the early stage of gene drive research in Australia and internationally, the Regulator recommends keeping a watching brief on work with organisms containing GM gene drives. Increasing the level of oversight for contained dealings with GM gene drive organisms would enable the Regulator to ensure appropriate risk management requirements are in place, and would permit information gathering as well as monitoring the progress of research in this rapidly developing field.

Further information about gene drives is at **Appendix D**. There are three components to a functioning gene drive using CRISPR technology: the drive, the payload and the target sequence. All three need to be present in the GMO in order for the gene drive to function. Non-functional gene drives are not preferentially inherited, therefore the recommended amendment is focused only on functional gene drive GMOs.

Dealings with GMOs containing functional gene drives would require a DNIR licence, which would ensure case-by-case evaluation of risks and tailored risk management of activities with these organisms. Case-by-case evaluation would take into account the risk-mitigating effects of molecular, environmental or physical containment approaches proposed in each case (eg split drives, daisy drives, synthetic targets).

Alternative approaches from submitters

As with the other aspects of new technologies, several submitters proposed alternative approaches to regulating contained dealings with gene drive GMOs.

One research submitter proposed a lower level of regulation than the recommended amendments, by applying the requirement for a DNIR licence to only a subset of contained dealings with gene drive GMOs, and allowing contained dealings with gene drive GMOs to continue as NLRDs if the gene drive utilises features that limit its ability to function in wild populations. This was proposed on the basis that it would provide an incentive for researchers to incorporate these features into their gene drive systems. Examples of these features include targeting synthetic sequences not present in unmodified organisms, or the “split drive” approach of locating gene drive components on different chromosomes, so they are not inherited together.

This would be a challenging approach to implement, as the GT Regulations would need to describe the features of gene drive GMOs that are suitable for NLRDs. Gene drive “safety features” are in an early stage of development and are an active field of research. An overly prescriptive approach could rapidly become outdated, raising the possibility of under-regulation of some gene drive GMOs (noting the time-frame needed to amend the GT Regulations).

Several community organisations and individual submitters proposed that all dealings with gene drive GMOs, including in containment, should be prohibited, on the basis that gene drive GMOs pose “potentially catastrophic ecological risks”. However, prohibiting dealings with gene drive GMOs is not possible within the current regulatory framework established by the GT Act, in which the highest tier of regulation is case-by-case assessment through licence applications.

This recommended interim measure would allow the Regulator to collect more information on the development of this technology and the risks involved in dealings with gene drive GMOs. It would be appropriate to re-assess this position at the next Regulations review on the basis of any accumulated experience and scientific developments at that time.

The Scheme Review has also considered the place of gene drive GMOs in the regulatory scheme, with the Preliminary Report (Finding 7) observing that “There is an identified need to determine the most appropriate approach for regulating the environmental release of genetically modified gene drive organisms (as well as any additional requirements for contained work).” This may lead to future consideration of whether changes to policy settings are needed to address issues raised by gene drive GMOs, particularly in the context of intentional environmental releases.

2.2.2 Cloned viral genomes

Dealings with cloned viral sequences, when at least one gene essential for viral multiplication is missing, are classified as exempt because they cannot result in the production of infectious agents. However, some cloned full length viral genomes are also unable to produce infectious agents unless additional non-host genes or gene products are provided. Dealings with these full length clones pose directly equivalent risks and so amendments are recommended to classify these as exempt, provided the required non-host genes or gene products are not available during the dealing. In both cases, risks associated with production of replication competent virus are avoided.

No change is proposed for cloned viral genomes which are able to give rise to infectious agents when introduced into a host cell. These cloned viral genomes,

commonly referred to as infectious clones, would continue to be regulated as if they were the virus itself.

2.2.3 Viral Vectors with no host

OGTR's interactions with IBCs and researchers indicate there is currently a lack of clarity about the classification of dealings with virions with no host. The recommended amendments would resolve this by classifying these dealings at the same level as dealings involving the introduction of these vectors into listed exempt hosts. Where viral vectors are themselves GMOs, dealings with these vectors without a host would be listed as exempt dealings, provided other existing requirements for exempt classification are met. This would be limited to virions of replication defective viral vectors unable to transduce human cells, specified GM baculovirus genomes or virions, and specified GM bacteriophage genomes or virions.

These amendments are not intended to change the classification of any dealings, instead they are intended to aid IBCs in their decision-making by improving clarity.

2.2.4 New exempt hosts

OGTR has received requests to list several hosts as suitable for exempt dealings, which have not previously been considered for listing. Risk assessments support two host species being added to the list of host/vector systems for exempt dealings as both species have no history of causing harm to people, animals, plants, fungi, or the environment: *Zymomonas mobilis* and *Corynebacterium glutamicum.*

2.2.5 Clarifying wording around characteristics of modifications

The categorisation of some contained dealings in Schedule 3 depends upon the characteristics of products encoded by inserted genes. However, the same phenotypic outcome can be produced by other modifications which don't involve the introduction of full gene sequences. Therefore, the recommended amendments would change some of the wording around pathogenic determinants and introduced DNA to shift the focus of the categorisation towards the outcome of the modification (e.g. immunomodulatory effects, ability to cause harm) rather than the characteristics of the introduced sequences. This would ensure the appropriate classification of dealings involving modifications other than the introduction of DNA, such as deletions, small changes in nucleotide sequence and the introduction of sequences that induce RNAi. This would avoid dealings being classified at a lower level than is appropriate for the risks they may pose.

2.2.6 Risk group requirements

The previous review of the GT Regulations in 2011 introduced a new category of NLRD for dealings with risk group 3 micro-organisms and required a licence for all dealings with risk group 4 micro-organisms. This has led to some stakeholder confusion as to how these provisions should be applied, and whether the effect of the modification should also be taken into account when assessing the risk group of the GMO. The intent of the 2011 amendments, as described in the explanatory statement, was that the relevant risk group is that of the unmodified parent organism. The recommended amendments include new clauses to clarify this.

These amendments would ensure that GMOs with risk group 3 or 4 parent organisms receive increased oversight or would be required to be undertaken in increased containment, as was intended when previous amendments were made. This would apply regardless of whether research organisations consider the modifications reduce risk grouping compared to the unmodified parent organism.

Several submitters opposed these amendments out of concern that they would down-grade the classification of higher-risk modifications on the basis of parent organism characteristics. However, these amendments would not alter the status of organisms carrying higher-risk modifications (see above discussion of the characteristics of modifications). Modifications that increase the risk grouping of a GMO compared to the unmodified parent organism are already addressed through categories of NLRDs and dealings that are not NLRDs.

2.3 Organisms derived from GMOs that are not themselves GMOs

The definition of 'GMO' in the GT Act does not include organisms derived from GMOs that have not inherited traits that occurred because of gene technology, also known as null segregants. Queries to OGTR suggest this status is not readily apparent to all, so the recommended amendments would list null segregants as organisms that are not GMOs, for the avoidance of doubt. For the same reason, organisms temporarily modified using gene technology that no longer have traits that occurred because of gene technology would also be listed as organisms that are not GMOs.

These listings would provide additional clarity that neither of these groups of organisms are within the intended scope of regulation. Neither group poses risks as a result of gene technology because, by definition, they do not possess traits as a result of gene technology. In this context a trait includes a modified sequence or an outcome that occurred because of genetic modification (for example, expression of a novel protein), and includes both intended modifications and unintended modifications (for example, secondary insertions).

Issues raised by submitters

Several submitters questioned the applicability of these amendments to organisms that have undergone SDN techniques, noting that some of these organisms are null segregants for SDNs stably integrated in parent generations. However, as these organisms carry genome sequence modifications (i.e. traits) that occurred because of gene technology, they would be GMOs.

Several submitters suggested either defining the term "trait" or avoiding its use in favour of describing the intended effect. However, usage of the term directly reflects its usage in the definition of "genetically modified organism" in the GT Act. The primary legislation would therefore be the appropriate place to define the term, and amending the GT Act is not possible through the Technical Review.

Some submitters opposed this proposal on the basis that it would "deregulate" organisms that are GMOs. However, these amendments would not change the regulatory status of any organisms, and are recommended only for the avoidance of doubt. Organisms derived from GMOs that do not have traits that occurred because

of gene technology are currently outside the scope of regulation, and would remain so even if these proposals did not proceed.

3. Impact analysis

Australia's gene technology regulatory scheme has been operating for over 16 years with the requirements of the scheme well established, and a very high level of compliance demonstrated by individuals and organisations working with GMOs. The scale of the gene technology regulatory scheme is modest in comparison to other Australian regulatory regimes. There are a limited number of regulated stakeholders, with 167 accredited organisations and 25 other organisations as at June 2018. Additionally, over 97% of authorisations for dealings with GMOs over the last five years have been for NLRDs, a category imposing minimal regulatory burden.

The recommended amendments outlined in this document do not propose to change the policy settings of the regulatory scheme or change the requirements for authorisation categories. Rather, the primary aim is to improve clarity and bring the GT Regulations up to date with scientific developments.

The costs and benefits for stakeholders of retaining the current GT Regulations, proceeding with the recommended amendments, or implementing alternative approaches put forward by submitters is analysed below in relation to the three key issues identified in Section 1. These impacts are primarily on organisations and individuals working directly with the described technologies, and by association (but to a lesser extent) the industry bodies that represent them.

Minor administrative amendments (outlined at **Appendix A**) are not discussed below as these are not anticipated to result in operational changes, and no submitters identified regulatory burden or other impacts from these proposals.

3.1 Impact of retaining the current GT Regulations

The likely impact of retaining the GT Regulations in their current form, with ambiguities in the legislation and out-of-date provisions remaining, is that risks related to these ambiguities (as described in the 'What are the risks' subheadings in Section 1) will continue. This includes:

- Continuing uncertainty regarding the regulatory requirements for activities with certain organisms, which may impact on research progress and investment. This could slow industry development and reduce international competitiveness.
- Regulatory classifications that are not up to date can impose over-regulation (impacting stakeholders by imposing unnecessary regulatory burdens, which can lead to reduced investment and research and development outcomes), or under-regulation (potentially leading to unmanaged risks to human health and safety and the environment).
- Ambiguity in the legislation could undermine the ability of the Regulator to enforce compliance, as well as impact the ability of organisations or individuals to comply with legal requirements.
- In the longer term, continuing uncertainty would undermine confidence in the gene technology regulatory scheme, as evidenced by the frustration expressed by some regulated stakeholders that the legislation has not kept pace with technological developments.

The vast majority of submitters to the Discussion Paper and amendment proposals consultations that identified a preferred way forward did not support retaining the current GT Regulations, on the basis that this would perpetuate uncertainty. Researchers have submitted that the current ambiguity makes planning research difficult, and introduces inefficiency and uncertainty into organisational governance of low-risk contained work. Companies and industry organisations have described the current uncertainty as a barrier to commercialisation, noting the difficulty of making investment decisions in an uncertain legal and regulatory environment.

Several submitters questioned the utility of amending the GT Regulations through the Technical Review when the concurrent Scheme Review is likely to address the same underlying issues raised by technological change. As discussed in Section 1.1, Finding 3 in the Scheme Review Preliminary Report would support further examination of key definitions, which is likely to take a considerable time to implement. Retaining the current GT Regulations while this proceeds would exacerbate existing uncertainty, because organisms developed using SDN techniques and ODM are progressing towards commercialisation. For example, the US company Cibus is marketing herbicide tolerant canola developed using ODM in north America, and DowDuPont has announced plans to commercialise waxy corn developed using SDN techniques in the same market in coming years. At the same time, Australian research organisations such as Agriculture Victoria are actively developing applications for Australian agriculture.

3.2 General impacts of amending the GT Regulations

Any amendments to the gene technology legislation have a transitional impact on those organisations working with GMOs, who need to become familiar with and implement any changes relevant to their organisation. This would be the case if the recommended amendments proceed in full or in part. As with previous technical reviews of the GT Regulations, OGTR would assist this transition by providing easily-understood guidance material and responding to queries as needed.

Organisations would need to access information about the amendments provided by OGTR then take stock of the authorisations they hold to establish if any new authorisations are required, or if any authorisations are no longer required. The transitional impacts of recommended amendments to the GT Regulations would be limited to organisations undertaking contained GMO dealings, as the amendments only alter the categorisation of certain contained dealings or alter the status of organisms that are currently only used in contained dealings (i.e. organisms modified using SDN-1 and RNA-delivered RNAi).

One hundred and thirty organisations hold current DNIR licences and/or have reported NLRDs to the Regulator in the previous five annual reporting periods[7]. Of the 123 organisations reporting 4105 NLRDs in this period, the number of NLRDs per organisation ranges from one to 359, with a median of eight. OGTR considers this number an over-estimate of the true number of active NLRDs because some dealings would have ceased before the five year NLRD time limit. In addition, OGTR is aware that a minority of organisations choose to re-assess NLRDs more frequently

[7] NLRDs may be conducted for a period of 5 years from the date of IBC assessment. NLRDs assessed in each annual reporting period must be reported to the Regulator in the three months following the end of that reporting period. Reporting periods are aligned to financial years. At the time of this analysis the Regulator had not received reports on NLRDs assessed by IBCs in the 2017-18 financial year, and data from the 2012-13 to the 2016-17 reporting periods was analysed.

than is required under the GT Regulations, to strengthen their internal oversight of research. This would lead to duplicate reporting of some NLRDs. Of the 46 organisations holding the 119 current DNIRs, the number per organisation ranges from one to ten, with a median of one.

It is difficult to predict the time necessary for organisations to review this stock of contained dealings, and no submitters provided specific information to support estimates. One regulated organisation identified a “moderate impact” from the need to review their authorisations, while another regulated organisation stated that the anticipated costs associated with updates to the GT Regulations have already been budgeted into normal business operations. Several other regulated organisations and a researcher stated they did not anticipate any additional burden from the amendment proposals.

OGTR estimates that, for a regulatory affairs specialist or IBC secretary already familiar with regulatory requirements, it may take up to one hour per organisation to access OGTR’s information about the amendments and up to one minute to review each authorisation. This gives an estimated total cost across all organisations of $12,912. For those organisations that choose to review authorisations more frequently than five-yearly, this review activity would represent a lesser burden beyond business as usual. The additional regulatory burden for obtaining any new authorisations required is considered below for each amendment proposal.

The recommended amendments include transitional provisions to minimise the disruption to regulated organisations:

- The amendments would commence in stages, starting at 6 months after registration of the made amendments. This would allow organisations time to become informed about the changes before they commence. It also allows time for States and Territories to amend their gene technology legislation as needed (i.e. in Victoria, Australian Capital Territory, South Australia and Western Australia, where the Commonwealth legislation is not automatically adopted), so as to ensure there is national uniformity.
- Contained GMO dealings that require a higher level of authorisation under the amendments would be allowed to continue under existing authorisations for a further year after the amendments commence. For GMO dealings that move from exempt to NLRD, from PC2 to PC3 NLRD, or from NLRD to DNIR, this would allow the dealings to continue while organisations seek the appropriate approvals.
- Amendments to NLRD governance and reporting would commence at the start of the 2019-20 reporting period. This would minimise disruption by ensuring all NLRDs assessed within a reporting period are subject to the same governance and reporting requirements.

These transitional provisions would provide organisations the time to plan and seek the approvals they will need, and as a result OGTR considers there will not be delay costs to regulated organisations.

3.3 Addressing ambiguities in the GT Regulations due to technological developments

As outlined in section 2.1, the recommended amendments include provisions to address ambiguities that have arisen because of technological developments, which would:

- clarify that organisms modified using SDN-2 and ODM are GMOs
- list organisms modified using SDN-1 as organisms that are not GMOs
- list RNA-delivered RNAi techniques as not being gene technology and
- replace item 1 of Schedule 1.

As discussed in Section 2.1.4, submitters who did not support the full package of recommended amendments to address technological developments supported two alternative approaches to regulating new technologies, reflecting their divergent underlying views on how GMOs should be regulated:

- Those seeking more oversight, through regulation of all organisms modified using new technologies, including SDN-1 and RNA-delivered RNAi. Two community groups, an organic agriculture organisation and some individual submitters supported this view.
- Those seeking reduced oversight of new technologies did not support amendments clarifying that organisms modified using SDN-2 and ODM are GMOs; they considered that a subset of these organisms, particularly plants, bearing modifications similar to those possible through conventional breeding approaches should not be regulated as GMOs. Six submitters predominantly from industry supported this view.

Implementing these alternate approaches and also gaining clarity could only be accomplished by developing further amendments to support each approach. The potential impacts discussed in Sections 3.3.2 and 3.3.3 below assume such clarity would be gained, and focus on how impacts would differ from the recommended approach.

3.3.1 Impact of recommended approach

The recommended amendments potentially impact several stakeholder groups, as discussed below.

Researchers

The recommended amendments are anticipated to improve efficiency for researchers by enabling organisations and individuals undertaking research using these technologies to confidently determine the regulatory requirements that they must comply with, saving them time (and therefore money).

Submissions from research organisations strongly support clarifying the legislation, and anticipate “considerable benefit” from improved clarity because they would spend less time determining regulatory requirements. With greater clarity, research may proceed more freely because researchers are no longer unsure about regulatory requirements. Additionally, the amendments would remove the risk that

some activities would mistakenly be undertaken without required approvals, protecting organisations or individuals from being liable for breaching the GT Act.

The recommended amendments are also anticipated to strengthen researchers' confidence that the regulatory scheme is commensurate with risk, and their confidence that OGTR is responding to technological developments appropriately.

These amendments would remove regulatory oversight of some research work involving new technologies, however OGTR anticipates this will not immediately change regulatory burden for the research sector. This is because the research that would no longer be regulated under the GT Act is generally integrated with work that would continue to require regulatory approvals, and this is anticipated to be the case for the foreseeable future. No submitters identified NLRDs that solely involve organisms to be excluded from regulation, or facility certifications that would no longer be required. To date OGTR has received no licence applications (DNIR or DIR) for relevant work.

Industry/product developers

Industry submitters anticipate economic benefits from the recommended amendments. Clarifying that organisms modified using SDN-1 are not GMOs and some RNAi techniques are not gene technology is expected to lead to increased innovation and increased commercialisation of related products (such as food crops or human or animal therapeutics), because of reduced regulatory costs and anticipated increased consumer acceptance of product that are not GMOs. Two submitters outlined current research investment in this area, and others stated that reduced resources would be required to bring SDN-1 products to market. However, none quantified these economic effects in terms of a number of products or specific other benefits.

Industry submitters to the Discussion Paper indicated ambiguity was a cause of delays in making investment decisions and taking up new technologies, including SDN-2 and ODM. However, in response to consultation on the recommended approach of regulating organisms modified using SDN-2 and ODM, industry submitters indicated that further barriers to commercialising products from these technologies would remain, namely regulatory costs and anticipated poor market acceptance of products identified as GMOs. Further, some industry submitters implied that commercialisation would only proceed if products have non-GMO status.

One submitter from the organic agriculture sector expressed strong concern about potential negative impacts on exports of Australian organic produce as a result of any move to reduce the scope of GMO regulation. However, many aspects of organic standards successfully operate without relying upon agricultural, environmental or food regulatory requirements. For example, the National Standard for Organic and Bio-Dynamic Produce (the mandatory Australian standard for exporting products labelled as organic) allows use of only some of the pest and disease control products for plants and animals approved under the Agricultural and Veterinary Chemicals Code.

Should the recommended new technologies amendments differ from organic standards in importing countries, exporters could utilise the mechanisms already in use where organic standards set stricter requirements than regulatory systems (e.g. documentation, assurances from suppliers).

The same organic industry submitter and several community groups expressed concern about possible impacts on Australian exports of agricultural commodities should key importing jurisdictions decide upon different regulatory approaches. Other industry submitters did not express views as to impacts on exports. Jurisdictions have also expressed interest in possible impacts on export markets, with the then South Australian Minister for Agriculture Food and Fisheries requesting this be considered, and the Tasmanian Minister for Primary Industries and Water's submission on the Discussion paper noting the importance of Tasmania's ongoing ability to market produce as GMO-free.

The position most other international jurisdictions will take on these technologies is yet to become clear. Canada's product-triggered regulatory system requires oversight of "plants with novel traits", whether these are produced using gene technology, mutagenesis, conventional breeding or SDN techniques. In August 2016 New Zealand's GMO regulatory framework was amended to clarify that organisms modified using SDN techniques are subject to regulation as GMOs. There have been further developments in other jurisdictions since November 2017:

- Chile and Brazil have recently (November 2017 and January 2018, respectively) established procedures for applicants to seek a case-by-case decision on whether crops developed using new technologies are GMOs, similar to the procedure in place in Argentina since 2015. In November 2017 Argentina broadened its procedure to also include animals. OGTR's understanding is that these frameworks require case-by-case consideration of organisms focusing on whether there is a new combination of genetic material, and that crops modified using SDN-1, SDN-2 and ODM would generally not be GMOs.
- In March 2018 the United States Department of Agriculture (USDA) issued a statement clarifying that USDA does not regulate plants with deletions, single nucleotide substitutions, insertions from compatible plant relatives or null segregants, unless plant pest species are involved. This means the majority of SDN-1 and ODM outcomes and some SDN-2 and -3 outcomes in plants are outside USDA's regulatory scope. This is a different approach to a US Food and Drug Administration (US-FDA) proposal in relation to animals with "intentionally altered genomic DNA", which has not yet been finalised. In the first half of 2017 US-FDA consulted on draft guidance that would expand its scope of regulation to include all animals modified using SDN techniques.
- On 25 July 2018, the Court of Justice of the European Union handed down a decision that the European GMO Directive is applicable to organisms modified by all of the new technologies OGTR has considered in the Technical Review. This was in response to a case brought against French authorities by several farmer groups. While the decision provides a legal interpretation of the GMO Directive, the European Commission is yet to indicate how it will be implemented. It is also too early to ascertain how jurisdictions within the European Union will approach the issues raised by the decision. The court considered that "risks linked to the use of these new mutagenesis techniques might prove to be similar to those that result from the production and release of a GMO through transgenesis". This accords with the Technical Review finding that some organisms modified using SDN-2 and ODM may pose novel risks that warrant regulation.

As more jurisdictions consider how they will approach new technologies within the context of their differing regulatory frameworks, it may take some years for global

trends to emerge. However, OGTR remains active in international discussions on this topic.

In this context, non-alignment between Australia and some trading partners appears likely, regardless of the direction of the Technical Review or further developments resulting from the Scheme Review. In the event this occurs, industry would have access to the same mechanisms used to resolve non-alignment issues for other aspects of trade.

Industry submissions and OGTR's experience indicate that excluding organisms modified using SDN-1 from regulation will not immediately change regulatory burden on industry stakeholders, because there are no DNIR, field trial or general release approvals for organisms that would no longer be regulated as GMOs. There would be no regulatory burden impact from clarifying that organisms modified using SDN-2 and ODM are GMOs because this would continue the current regulatory status of these organisms.

As a comparison point for regulatory burden impact analysis, it appears likely that few, if any, products utilising SDN-1 or RNA-delivered RNAi would be commercialised if the current ambiguous legislation remained in place. That is, regulatory burden is currently low because activity is low. While it is not possible to estimate the uptake of these technologies in future should the recommended amendments proceed, current indications are research activity would increase. However, regardless of the level of activity, regulatory burden would remain low because these activities would be removed from the scope of regulation. As a result, the amendments are likely to have minimal impact on regulatory burden.

Similarly, repeal and replacement of item 1 of Schedule 1 is not anticipated to have any regulatory burden impact, and the only other impacts would be as a result of improved clarity. As noted in the Discussion Paper, item 1 is a source of much uncertainty because it contains several undefined terms; some stakeholders interpret this item as excluding some SDN techniques from regulation.

Historically, OGTR is aware of two organisms excluded from regulation under item 1, and the status of these organisms would be maintained through replacement items on Schedule 1 referring specifically to the organisms. No other organisms were identified through consultation on the proposed amendments, however, should these come to light, organisations would have a transitional period of 18 months after the amendments are made to seek appropriate authorisation for GMO dealings. While several submitters expressed concern that repealing item 1 would impact the status of organisms mutagenised using chemicals or radiation, these techniques would remain listed as techniques that are not gene technology in Schedule 1A, with the result that organisms modified using these techniques would continue to be excluded from regulation.

Members of the public

It is not expected that there will be any direct impact from the recommended amendments relating to new technologies on members of the Australian public. Individuals and community groups have expressed concern about the implications of this review for food labelling (i.e. their ability to choose to avoid GM foods) and the pre-market safety assessment of GM foods by FSANZ. However, the recommended amendments would not alter the regulation of GM food in Australia, including how

such foods are labelled. These matters are outside of the scope of the GT Regulations and are being considered separately by FSANZ[8].

For the majority of the public, efforts to keep the gene technology legislation up to date with scientific developments may improve their confidence that regulatory oversight is effectively protecting human health and safety and the environment. However, for those with strong concerns about the safety of GMOs and GM foods, including the majority of the individual submitters to the review, the recommended amendments may reduce their confidence in the regulatory system, because some technologies and organisms would be removed from the scope of the regulatory scheme. A 2017 survey of community attitudes to gene technology commissioned by OGTR[9] concluded that about 13% of the Australian population is strongly opposed to GM foods and GMOs, a figure which has not changed substantially over recent years.

A broader impact that may result from providing certainty to industry is that consumers may be able to access beneficial new products that reach the Australian market.

3.3.2 Impact of increased oversight of new technologies: regulating organisms modified using SDN-1 and RNA-delivered RNAi

OGTR's Discussion Paper consultation canvassed the option to regulate organisms modified using SDN-1, SDN-2 and ODM, which was not developed further as an amendment proposal (see Section 2.1.4). However, some submitters on the amendment proposals consultation reiterated their support for regulating all new technologies, extending this to RNA-delivered RNAi (which was not part of the Discussion Paper options). Regulating all organisms modified using new technologies differs from the recommended amendments by seeking to regulate organisms modified using SDN-1 and RNA-delivered RNAi, and the impact of this approach is discussed below only in relation to this difference.

This approach is anticipated to reduce uptake of SDN-1 and RNA-delivered RNAi by industry, similarly to the impact discussed above in relation to regulating SDN-2. Some industry submitters implied that commercial applications of new technologies in general would only proceed if the resulting products have non-GMO status, and it is reasonable to assume they would extend this comment to SDN-1 and RNA-delivered RNAi.

OGTR anticipates that this approach would significantly undermine confidence in the regulatory scheme amongst researchers and industry, many of whom support regulation only where it is necessary to manage risks. Many industry and research submitters supported OGTR's analysis that organisms modified using SDN-1 and RNA-delivered RNAi do not pose risks that warrant regulating these organisms as GMOs. Through the Discussion Paper consultation a similar approach was supported by only five of 40 research sector submitters and only two of 21 agriculture-related submitters (both of these were from the organic agriculture sector).

[8] In February-April 2018 FSANZ held a public consultation for a review considering how the Australia New Zealand Food Standards Code applies to food derived using new technologies. Further information is available on the FSANZ website.

[9] "Community attitudes to gene technology" by Craig Cormick and Rob Mercer, available on the OGTR website.

Regulating organisms modified using SDN-1 and RNA-delivered RNAi is not anticipated to immediately increase regulatory burden, on the basis that there are no current licences for dealings with these organisms. Similarly to SDN-2, contained dealings with organisms modified using SDN-1 are likely to be integrated in research projects also involving GMOs, and so NLRD authorisations would already be necessary.

3.3.3 Impact of reduced oversight of new technologies: excluding organisms modified using SDN-2 and ODM from regulation

OGTR's Discussion Paper consultation canvassed the option to exclude organisms modified using SDN-1, SDN-2 and ODM from regulation, which was not developed further as an amendment proposal (see Section 2.1.4). However, some submitters on the amendment proposals consultation reiterated their support for this approach. Excluding these organisms from regulation differs from the recommended amendments by also seeking to exclude organisms modified using SDN-2 and ODM from regulation, and the impact of this approach is discussed below only in relation to this difference.

The approach advocated by submitters seeking reduced oversight of new technologies can not be achieved in a way that is commensurate with risk and also in keeping with the policy settings of the regulatory scheme. The current policy settings do not establish scope to exclude some classes of organisms that have undergone a modification process from regulation (e.g. plants), while retaining regulation of others that have undergone the same process (e.g. pathogenic microbes)[10]. Similarly, excluding a product class (organisms with modifications similar to those possible through conventional breeding approaches) is not consistent with the process-focussed definition of GMOs in the GT Act. As a result, implementing this approach would remove regulatory oversight of some organisms that many research submitters consider should be regulated as GMOs. In turn, this is likely to undermine the confidence researchers and members of the public have that the regulatory scheme is appropriately addressing risks.

This approach would remove the barriers to commercialisation identified by industry submitters, and likely result in greater development of commercial products derived using SDN-2 and ODM. Similarly to the recommended amendments, the impact on regulatory burden of this approach is likely to be small. In comparison to the low current level of activity with SDN-2 and ODM organisms as NLRDs, any new activities as a result of amendments to reduce oversight excluded would be outside the scope of regulation.

3.4 Updating the categorisation of contained dealings with GMOs

3.4.1 Impact of recommended amendments

As outlined in Section 2.2, the recommended amendments include provisions to adjust the level of regulation of some contained dealings with GMOs to be more commensurate with risk:

[10] The policy settings in this area that constrain the Technical Review are being considered through the Scheme Review.

- increase the categorisation of contained dealings with gene drive GMOs from NLRDs to DNIRs
- increase the categorisation of contained dealings with GMOs that have pathogenic or oncogenic effects brought about other than through expression of a protein with these properties, some from exempt to NLRD and others from NLRD to DNIR
- decrease the categorisation of some contained dealings with *Zymomonas mobilis* and *Corynebacterium glutamicum* from NLRD to exempt
- decrease the categorisation of some contained dealings involving cloned viral genomes from NLRD to exempt
- clarify the categorisation of dealings involving viral vectors with no host and
- clarify the categorisation of dealings with GMOs with risk group 3 or 4 parent organisms.

These amendments are anticipated to primarily impact research organisations where contained GMO dealings are being undertaken. The amendments would improve research organisation's confidence that regulatory burden from the gene technology regulatory scheme is commensurate with risk, and improve compliance with regulatory requirements by making those requirements clearer.

The short-term regulatory burden impact of these proposals is anticipated to be minimal and limited to only those organisations undertaking contained research with the relevant GMOs. These organisations would experience variable small increases and decreases in regulatory burden, depending upon the work they undertake.

Requiring case-by-case evaluation of risks and tailored risk management for contained activities with GM gene drive organisms may increase confidence for the Australian population and amongst regulated organisations that risks posed by contained research with these organisms are being appropriately managed. One research organisation identified one NLRD that would require a DNIR licence as a result of the recommended amendments. The other research organisation that OGTR is aware is undertaking contained dealings relating to gene drive GMOs did not identify any change to regulatory burden.

While there are no fees to submit a DNIR application, additional information is required by the Regulator compared to what is required for NLRDs. In comparison to NLRDs, additional time is necessary for researchers to prepare a DNIR application, for IBC oversight of applications, and for organisations to meet licence requirements. No submitters provided information to substantiate the regulatory burden cost of NLRDs or DNIRs. Based on available information and reasonable assumptions, the average administrative cost to organisations per NLRD authorisation is $313, and per DNIR is $5366 (noting DNIRs vary widely in their complexity). If two current NLRDs would require DNIR authorisation under the recommended amendments, this is estimated to increase regulatory burden by a total of $10,106 across two organisations.

The early stage of gene drive research makes it impossible to predict the scale of future research projects involving functional gene drive GMOs, and so it is not possible to estimate regulatory burden impacts into the future. The number of future projects will depend upon the findings of international research expected to explore

the effectiveness of gene drives in coming years. Should the effectiveness of gene drives be demonstrated, the rate of Australian uptake will depend upon interest in developing gene drive applications specific to Australian needs. This in turn will be influenced by social acceptance of this technology, and the future regulatory landscape for environmental releases of gene drive GMOs[11]. DNIR licences are typically approved for five-year periods, and so if the two current gene drive projects were to continue over the coming 10 years, the total cost to those organisations of maintaining DNIRs rather than NLRDs is estimated to be a further $10,106, noting that a second application on the same topic is generally less time-consuming to prepare than an initial application.

Other amendment proposals are anticipated to lead to smaller regulatory burden increases than the gene drive amendment, or possibly a small decrease in regulatory burden. Submissions have not brought to light any current contained GMO dealings that would require a higher level of authorisation or containment than is currently required, other than the single gene drive NLRD discussed above. In relation to each group of proposals, the following likely regulatory burden impacts have been identified:

- Re-wording descriptions of pathogenic/oncogenic effects is not expected to change regulatory burden, on the basis that OGTR understands regulated organisations have already been following the spirit of these provisions (i.e., they are already applied to organisms with these particular risk features, regardless of how the organisms were modified); no submitters identified any specific impacts.
- Adding two new exempt hosts is expected to reduce burden where these organisms are currently used in NLRDs, as such work would predominantly become exempt dealings. However, no submitters identified any current impacts, and the two organisations requesting the listings did not make submissions. As of June 2018 there was one NLRD reported to OGTR referring to these organisms.
- Decreasing the classification of some work with cloned viral genomes is expected to allow some research to be undertaken as exempt dealings rather than NLRDs, however no submitters identified any current impacts.
- Clarifying the categorisation of dealings involving viral vectors with no host is not anticipated to change regulatory burden because it is not intended to change the categorisation of any dealings. However this amendment is anticipated to make it easier for organisations to understand the regulatory requirements.
- Clarifying the categorisation of dealings with risk group 3 (RG3) and RG4 GMOs may result in a minor increase in burden for organisations working with these organisms that have interpreted current provisions in a different way. One submitter organisation identified that they would need to replace some NLRDs with DNIRs, but this was retracted upon OGTR seeking further detail and providing more information about the amendment proposals. No other organisations identified a need for additional approvals. There are 16 PC3 NLRDs in the last five annual reporting periods, and several current DNIRs

[11] Finding 7 of the Preliminary Report for the Scheme Review indicates further policy consideration is likely to be given to approaches to regulate environmental release of gene drive GMOs and contained dealings.

involving RG3 and RG4 organisms. Following consultation, this amendment proposal was altered to specifically exclude lentiviral vectors addressed through specific PC2 NLRD categories, for clarity.

Several research organisations submitted that amendments relating to contained dealings classification would not have a regulatory burden impact on their organisation.

3.4.2 Impact of alternative approach from submitter – gene drives

One submitter, a gene drive researcher, proposed only requiring a DNIR licence for contained dealings with gene drive GMOs that do not incorporate "safeguards" to limit their ability to spread through wild populations. The specific impact of this approach depends somewhat on what would be considered an appropriate "safeguard", however three key impacts are foreseeable:

- Introducing further technical detail into this amendment is likely to make it more difficult for researchers to determine the regulatory requirements that apply to them, particularly as the underlying methods develop in coming years.
- Imposing prescriptive requirements runs the risk that the legislation will rapidly become out-dated in the face of rapid scientific developments; as a result, higher risk organisms may not be subject to an appropriate level of oversight.
- Many research organisations have expressed support for the recommended amendment, and imposing a lesser level of regulation may undermine their confidence that the regulatory scheme appropriately responds to risk.

The regulatory burden impact of this proposal would be equal to or smaller than the modest impact of the recommended approach. Whether the two current gene drive NLRDs that OGTR is aware of utilise "safeguard" features is unknown to OGTR.

3.5 Impact of clarifying the regulatory status of organisms derived from GMOs

The recommended amendments to clarify the status of some organisms derived from GMOs would not alter the regulatory status of these organisms, as described in section 2. Potential impacts from these changes include that the GT Regulations will become more efficient in that they will enable organisations and individuals working with these organisms to confidently determine the regulatory requirements that they must comply with.

There will not be any change to the regulatory burden on individuals and organisations working with these organisms, as the amendment would not change the status of any organisms, and no submitters identified regulatory burden impacts as a result of this proposal. Several community organisations, individuals and an organic agriculture body opposed this amendment and stated that these organisms, known as null segregants, should not be "deregulated". However, the amendment would only clarify their current status as outside the regulatory scheme. Imposing new requirements on null segregants would be contrary to the policy intent since commencement of regulatory scheme.

3.6 Comparison of options and conclusion

The Regulator supports the full suite of recommended amendments to the GT Regulations being made, to achieve the aim of the Technical Review.

The increased regulatory burden on regulated stakeholders as a result of the recommended amendments is estimated to total less than $24,000 in transitional costs and immediate changes in regulatory burden. This cost is out-weighed by the benefits of the recommended amendments in:

- enabling management of risks posed by GMOs without unnecessary impacts on stakeholders
- providing legal clarity and certainty to regulated stakeholders, industry and the Regulator while policy considerations raised through the Scheme Review are progressed, and
- maintaining confidence that the regulatory scheme is justified on a risk basis.

4. Consultation

This Technical Review of the GT Regulations has been undertaken through a transparent, consultative process. OGTR drew on the knowledge and experience of stakeholders to the regulatory scheme to develop the recommended amendments, through different stages of public consultation. Prior to the review direction being decided, views were sought through a formal public submission process and follow-up discussions with submitters. Further public consultation on specific amendment proposals has strengthened the resulting recommended amendments, and supported analysis of potential impacts.

4.1 2016 Discussion Paper consultation

From 17 October to 16 December 2016, the Regulator sought submissions from all interested and affected parties on a discussion paper detailing four options for how new technologies could be regulated. The Discussion Paper also sought input on a range of other topics related to the effectiveness of the legislative framework for the regulation of GMOs. This public consultation was undertaken to collect views and draw on expertise of stakeholders prior to OGTR developing amendment proposals, as there was a high level of stakeholder interest in the Technical Review.

Submissions were received directly from 125 individuals, research institutions, companies, industry associations, government bodies and community groups. A further 615 submissions were received from individuals through a web form set up by Friends of the Earth Australia on the Do Gooder web platform. A summary of the 741 submissions received from the Discussion Paper consultation process is available on the OGTR website along with the submissions.

The OGTR also undertook targeted consultations (face-to-face or by teleconference) with representatives of over 50 submitter organisations to further discuss issues raised in their submissions.

Issues raised in submissions were considered during the development of draft amendments following the 2016 consultation. The Regulator's considerations have also taken into account OGTR's experience, current scientific understanding, potential risks, regulatory burden implications for stakeholders, whether regulatory burden would be commensurate with risks, and the policy intent of the GT Act.

4.2 2017-18 Amendment proposals consultation

From 30 November 2017 to 21 February 2018 the Regulator sought submissions on draft amendments to the GT Regulations to address the problems identified in Section 1, asking:

- whether or not to progress the amendment proposals (in full or part)
- whether the drafting was effective in providing clarity
- what the costs and benefits to submitters from the amendment proposals may be
- whether proposals to change the classification of certain NLRDs and exempt dealings were commensurate with risk[12].

[12] This aspect of consultation was undertaken in accordance with Section 142 of the GT Act.

OGTR directly received submissions[13] from 40 members of the public and 45 organisations, including :

- research organisations and individuals working with GMOs
- companies working with GMOs in Australia and overseas
- States and Territories, and relevant Australian Government agencies and
- community and industry groups with an interest in gene technology regulation.

Comments from these submitters on specific amendment proposals are incorporated in the discussion of the proposals (Section 2) and their possible impacts (Section 3), with a summary of their views below. An additional 365 submissions were received from members of the public and a community group through a web form set up by Friends of the Earth Australia on the Do Gooder web platform. Three of these submissions were identical to submissions received directly.

Eighteen submitters came from the research sector, comprising research organisations, scientists' organisations and individual researchers. Two-thirds of these submitters supported the full package of amendment proposals. Two other research-related submitters preferred reduced oversight of new technologies, one preferred more oversight of new technologies, and the remaining three commented on specific technical issues.

Sixteen submissions were received from companies or industry organisations predominantly from agriculture, but also representing enzyme production, vaccine production (for human and veterinary applications), and biotechnology generally. Of the eleven submitters in the agriculture sector, four supported the amendments in full, four sought reduced oversight of new technologies, and one sought more oversight of new technologies. Of the five submitters from other areas of industry, two supported the amendments in full, two sought reduced oversight of new technologies, and one focused on specific technical issues.

Of the six government agencies that provided submissions, two-thirds supported the proposed amendments. The remaining two did not specify whether or not they supported the amendments. The five community groups that provided submissions expressed their desire for strong regulation of GMOs and views that no techniques or organisms should be excluded from regulation.

OGTR noted a lower level and depth of engagement in this consultation compared to the Discussion Paper consultation. The number of submissions received was lower, and fewer submitters identified a preferred option or directly answered the consultation questions. For example, even amongst direct submissions from organisations with an interest in GMO regulation, 38% did not identify a preferred option (compared to 12% for the Discussion Paper) and 64% did not directly address the consultation questions (compared to 28% for the Discussion Paper). Given the concurrent Scheme Review, which initiated its third round of consultation in March 2018, and consultation for a FSANZ review on this subject in February-April 2018, submitter fatigue is likely to have contributed to this outcome.

As was expected for consultation on the wording of amendments, many submitters focused on aspects of wording or interpretation and questioned the intended scope

[13] Submissions to the amendment proposals consultation are available on the OGTR website.

of the proposals. Input received on specific amendments and the impacts they may have is summarised in Section 3 of this document. Where drafting has been changed between the consultation and final versions of the recommended amendments, this is detailed in **Appendix C**. The issues raised in submissions also informs the Explanatory Statement to the recommended amendment regulations, which is intended to provide clarity about the intended scope and operation of the amendments. The queries and points of clarity raised by submitters will also be addressed through informal guidance material to be developed by OGTR and distributed to regulated stakeholders prior to the amendments commencing.

Of submissions received from individual members of the public, including through the Friends of the Earth Australia web form, approximately 30% submitted that new technologies should be regulated. These submitters expressed opinions on more general issues, with approximately three quarters supporting stronger regulation of GMOs and nearly half considering more research about GMOs and/or safety testing was needed. Nearly one quarter expressed general opposition to gene technology. Amongst this submitter group there were many misunderstandings that the Technical Review would lead to broad deregulation of GMOs or deregulation of all CRISPR techniques.

Many of these submitters raised issues beyond the scope of the Technical Review, with one third commenting on the need for GM food to be labelled to support consumers who wish to avoid GM foods. Regulation of GM food products, including labelling, is beyond the scope of the gene technology regulatory scheme. Amendments to the GT Regulations would not change the pre-market approval or labelling requirements for GM foods and ingredients in Standard 1.5.2 – Food produced using gene technology in the Australia New Zealand Food Standards Code, which is administered by FSANZ.

5. Implementation and Review

5.1 Next steps – updates to State and Territory legislation

If the LGFGT agrees to the amendments, the OGTR will commence the Commonwealth regulation-making process which requires approval from the Governor-General and tabling in Parliament. It is anticipated this could be undertaken in the latter half of 2018, allowing for commencement of amendments in 2019.

The bulk of the amendments would commence six months after making by the Governor-General, with this delay intended to allow jurisdictions time to update their gene technology legislation as necessary. No action would be needed in jurisdictions that automatically adopt amendments to the Commonwealth gene technology legislation (Queensland, New South Wales, Tasmania and the Northern Territory). Other jurisdictions (Victoria, the Australian Capital Territory, South Australia, Western Australia) would need to pass equivalent amendments to their gene technology regulations. Without these amendments, researchers operating in these jurisdictions would face differing legislative requirements depending upon whether their work is governed by Commonwealth or State gene technology legislation.

5.2 Assisting regulated organisations before commencement

The OGTR website is the first point of contact between many regulated organisations and the OGTR, and is the primary means for OGTR to provide information about legislative changes. As with previous amendments to the gene technology legislation, prior to the amendments commencing OGTR would provide comprehensive, accessible information through the website, and would directly notify accredited organisations and IBCs about the availability of this information and timing of the amendments commencing.

OGTR would continue to respond to telephone and email queries about regulatory coverage. OGTR also has regular contact with regulated organisations through application assessments and monitoring and compliance activities. Through these activities, OGTR would ensure regulated organisations are aware amendments are pending and provide information to support organisations in their transition.

5.3 Commencement of amendments

Staged commencement of the amendments and transitional arrangements are intended to minimise disruptions to those undertaking GMO dealings that are affected by the amendments. The amendments would commence in three stages:

- 6 months after making: the majority of amendments would commence at this time, with OGTR providing information to regulated organisations in the 6 months prior to commencement. Dealings for which the level or type of authorisation would change would be allowed to continue under pre-existing authorisations for up to one year, while new authorisations are sought.
- 1 July 2019: minor amendments to NLRD assessment and reporting requirements would commence at the start of the NLRD annual reporting period, so as to ensure requirements do not change part-way through a reporting period.

- 18 months after making: repeal of an item on the list of “organisms that are not GMOs” would occur, to allow sufficient time before commencement for organisations to obtain new authorisations, if any are necessary.

5.4 Future Technical Reviews

Two issues requiring future consideration have been identified through the current review, as described below.

The recommended amendments include requiring a licence for contained dealings with gene drive GMOs as an interim measure while knowledge of this technology develops. This position should be reassessed at the next technical review of the GT Regulations on the basis of accumulated experience and scientific developments at that time.

Early development of a new application of CRISPR-Cas9, known as base editing, has emerged during this review, as discussed in Section 2.1.4. Base editing techniques are currently developing rapidly and at this time there is insufficient knowledge to determine whether or not they should receive the same regulatory status as SDN-1, as has been suggested by some submitters. Base-edited organisms should be considered at the time of the next technical review of the GT Regulations, in light of further developments and scientific understanding at that time.

This is the third technical review of the GT Regulations undertaken by the Regulator. OGTR recognises that regular reviews are needed to keep technical aspects of the legislation up to date with technological progress and changes in scientific understanding of the risks posed by gene technology. Future reviews will be needed to ensure the legislation remains up to date, and to maintain confidence amongst stakeholders that the regulatory scheme is commensurate with risk.

Glossary

Term	Definition
COAG	Council of Australian Governments – the peak intergovernmental forum in Australia.
DIR	Dealings involving an Intentional Release of GMOs into the environment – all GMO dealings outside contained facilities require case by case assessment and licencing from the Regulator, from small field trials to general releases.
DNIR	Dealings Not involving an Intentional Release of GMOs into the environment – work with higher risk GMOs that is undertaken in contained facilities such as laboratories and requires case by case assessment and licencing from the Regulator.
FSANZ	Food Standards Australia New Zealand – a statutory authority in the Australian Government Health portfolio. FSANZ develops food standards for Australia and New Zealand.
GMO	Genetically modified organism which has the meaning as provided in section 10(1) of the GT Act.
GM	Genetically modified – an organism, or product of an organism, that has been changed by gene technology.
GT Act	*Gene Technology Act 2000*
GT Regulations	Gene Technology Regulations 2001
IBC	Institutional Biosafety Committee – IBCs provide on-site scrutiny of NLRD proposals through independent of NLRD proposals.
LGFGT	Legislative and Governance Forum on Gene Technology – the ministerial committee with responsibility for oversight of Australia's gene technology regulatory scheme.
NLRD	Notifiable Low Risk Dealing – activities with GMOs undertaken in containment (i.e. not released into the environment) that have been assessed as posing low risk.
ODM	Oligo-directed mutagenesis – a process for making small, precise changes to a genomic DNA sequence using a short single stranded synthetic nucleic acid (DNA or RNA) called an oligonucleotide (oligo) as a template.
OGTR	Office of the Gene Technology Regulator – staff supporting the Gene Technology Regulator.
Regulator	Gene Technology Regulator – an independent statutory office holder responsible for administering the GT Act and corresponding State and Territory laws.
RIS	Regulation Impact Statement – an analysis of the costs and benefits of proposed changes to regulation, to support decision-makers.
RNAi	Ribonucleic acid (RNA) interference – a cellular mechanism that modulates gene expression and protects against viruses, which can be harnessed to reduce expression of proteins from targeted genes.

Term	Definition
SDN, SDN-1, SDN-2 and SDN-3	Site-directed nuclease – specially designed proteins, or protein/nucleic acid combinations, that are capable of cutting DNA at a specific nucleotide sequence. Techniques to modify sequences following SDN action include: • SDN-1 –non-homologous end-joining repair of DNA breaks resulting in small random sequence changes. • SDN-2 – homology directed repair of DNA breaks using an oligo to guide a specific small modification of one or several nucleotides. • SDN-3 – homology directed repair of DNA breaks using a large template to guide insertion of new sequences.

Appendix A: Recommended administrative amendments to the Gene Technology Regulations 2001

In addition to the recommended amendment proposals described in Section 2 the following administrative amendments are recommended. Refer to **Appendix B** to cross-reference these topics to provisions in the GT Regulations and amendment items.

Cross-references within Schedule 3

Parts 1 and 2 of Schedule 3 describe GMO dealings classified as NLRDs. Importantly, Part 3 (dealings which are not notifiable low risk dealings) qualifies the lists in Parts 1 and 2, so that a dealing of a kind described in Part 3 is not an NLRD even if it meets a description in Part 1 or Part 2. Dealings which do not meet the requirements for classification as exempt dealings or NLRDs must only be conducted if authorised by a licence issued by the Regulator. Proposed amendments to make the role of Part 3 more prominent are intended to ensure dealings are correctly categorised, and would not alter the categorisation of any dealings.

Suitability of facilities for NLRDs

Regulation 13(2) specifies the kinds of facilities suitable for undertaking different categories of NLRD. These considerations are relevant both during the IBC's initial assessment of the dealing (regulation 13B(a)(vii)) and also while the dealing is being conducted. The amendment proposals would clarify that IBCs must consider which facilities meet the suitability requirements at the time the NLRD is being assessed, and persons conducting NLRDs may only undertake NLRDs in suitable facilities, within the limits provided in the IBC record of assessment.

NLRD record of assessment and reporting requirements

The GT Regulations require that dealings IBCs assess to be NLRDs are notified to the Regulator. In recognition that instruments of accreditation provide a reporting requirement, including its timeframe, the timeframe for reporting for accredited organisations will be removed from the GT Regulations.

The GT Act allows for a 'person or persons' to undertake an NLRD, and the GT Regulations refer variously to organisations and accredited organisations in roles related to NLRDs. These references will be updated for consistency with the GT Act.

Importantly, the *Acts Interpretation Act 1901* provides that the term 'person' in legislation includes "a body politic or corporate as well as an individual". It is not intended that individuals would be named for NLRD reporting purposes; the name of a company or the description "members of X organisation" would meet the requirement.

NLRD time limits

Regulation 13A provides time limits for stopping NLRDs, with a phase-in of time limits for dealings assessed by an IBC before 31 August 2016. As this date has passed paragraphs (b) and (c) no longer serve a purpose and this Regulation can be removed, allowing the five year time limit to be placed through Regulation 13.

Use of the symbol µ for micrograms

The Greek letter 'mu' (µ) is used throughout the GT Regulations as part of a recognised international symbol indicating 'micrograms'. This symbol is usually displayed correctly, however some devices may display it incorrectly (in Word and possibly HTML and PDF), making units read as 'mg' (milligrams), which significantly changes the meaning of the legislation. The symbol would be replaced by the word 'micrograms'.

References to GM products

The *Gene Technology Amendment Act 2015* removed the requirement for the Regulator to maintain a record of GM product approvals made by other agencies. Remaining references to 'GM products' in the GT Regulations no longer serve a purpose or have any legal effect, and will be removed.

Out of date material, typographical errors and drafting style updates

The GT Regulations contain cross-references to provisions in the GT Act that have since been amended, a broken web-link, an out-dated agency name and several typographical errors. These would be corrected, and as necessary the drafting style would be updated to match current practices of the Office of Parliamentary Counsel (most notably the table in Schedule 2 Part 2).

Appendix B: Summary of recommended amendments to the GT Regulations

Topic area	**Amended provisions in the Gene Technology Regulations 2001**	**Amendment item in Gene Technology Amendment (2018 Measures No.1) Regulations 2018** (Schedule 1 unless noted otherwise)
Clarifying scope of Regulation - What is a GMO		
Organisms modified using SDN-1 are not GMOs	Schedule 1 – new item	Item 26
Organisms modified using SDN-2 and ODM are GMOs	4A – new, 5 Schedule 1B – new	Items 7, 8 and 25
Replacing Item 1 of Schedule 1	Schedule 1, item 1 and two new items	Schedule 1 item 27 Schedule 3
Some RNAi techniques are not gene technology	Schedule 1A – new item	Item 24
Organisms derived from GMOs	Schedule 1 – two new items	Item 27
Categorisation of Contained Dealings		
Gene drives	Schedule 3, 3.1(r) & (s) - new	Item 62
New exempt hosts	Schedule 2, Part 2 – within new Item 6	Item 33
Cloned viral genomes	Schedule 2, Part 1, item 4(2)	Item 31
Viral Vectors with no host	3 – definition of host/vector system and non-vector system Schedule 2 Part 2 2.1 – new Schedule 3, 1.1(c), 2.1 (c), (d), (i)-(m), 3.1 (d)	Items 2, 3, 33, 35, 37, 42-46, 48-51, 53, 58
Clarifying requirements for characterisation of modifications	3 –definition of characterised Schedule 3, 1.1(c), 2.1(d), (e), (k) & (m) and 3.1(d)-(f)	Items 1, 35, 38-40, 47, 52, 58-61
Clarification of risk group considerations	Schedule 3, 2.2(2) & (3) – new Schedule 3, 3.1(1)(q), (2)-(4) - new	Items 54, 56, 62

Topic area	**Amended provisions in the Gene Technology Regulations 2001**	**Amendment item in Gene Technology Amendment (2018 Measures No.1) Regulations 2018** (Schedule 1 unless noted otherwise)
NLRD Administration		
NLRD facilities	13, 13B Schedule 3, 1.1, 2.1	Schedule 1 items 13-15, 17, 18, 34, 36 Schedule 2 item 4
NLRD record of assessment	13(1)(e), 13B	Schedule 1 items 12, 16 Schedule 2 items 2, 3, 4, 5, 7
NLRD notification	13C, 39	Schedule 2 items 6, 8
Role of Schedule 3, Part 3 in categorising dealings	12(1)(a), 13(1)(b), and 13B	Schedule 1 item 10 Schedule 2 items 1, 3
NLRD time limit	13(1)(d), 13A	Items 11 and 19
Administrative changes		
Updating cross-references	21(2) note, 26(1)(b) and 32(c)	Items 20-22
Micrograms symbol	3 – definition of toxin-producing organism Schedule 2, Part 1, Item 4 Schedule 3, 3.1(a) & (b)	Items 4, 30, 57
Remove reference to GM products	note to 3, 39	Schedule 1 item 5 Schedule 2 item 8
Update to current styles	4, 5, Schedule 2, Parts 1 and 2 Schedule 3, 2.1(h), part 3 (note 2 to Part heading)	Items 6, 32, 33, 41, 55
Update agency name	9(f)	Item 9
Correcting typographical errors	Schedule 2, Part 2, item 4	Items 28, 29
Transitional provisions	Part 8 – new	Schedule 1 item 23 Schedule 2 item 9

Appendix C: Amendment drafting changes following consultation

Following consultation on draft amendment proposals in 2017-2018, the amendments were finalised to take into account issues raised in submissions and further minor matters raised through internal OGTR considerations.

New inclusions following consultation

Amendments to NLRD reporting were altered to introduce further flexibility in anticipation of a project to develop online NLRD forms becoming operational in coming years. Once online forms are fully operational, organisations would have the option to report NLRDs to the Regulator intermittently throughout the year, and annual reports from accredited organisations would either provide all NLRD notifications or certify that NLRD reporting has been completed. This would enable a new reporting method, while allowing organisations to continue using the current reporting method.

A new amendment to the note to Schedule 3 part 3 heading was included to correct an incomplete reference to authorisation types other than NLRDs (a clarification with no operational effect).

Clarifications with minor impacts on operation of amendments

In response to stakeholder queries about the relationship between the list of "organisms that are not GMOs" (Schedule 1) and the proposed list of "organisms that are GMOs" (Schedule 1B), an amendment to Regulation 5 was added to clarify that Schedule 1B has precedence over Schedule 1, should any organism meet items on both lists. This additional amendment would improve clarity, particularly in the period before repeal of Schedule 1 item 1.

OGTR and the Gene Technology Technical Advisory Committee identified that proposed amendments relating to risk group 3 (RG3) and RG4 organisms would, as then drafted, inadvertently affect the status of dealings involving GM viral vectors derived from these organisms (i.e. lentiviral vectors). The amendments were altered so as to maintain the status of dealings with these vectors where it is specifically addressed by PC2 NLRD clauses. As part of these considerations, clauses relating to the PC3 NLRD category and facility requirements for these NLRDs were restructured for better clarity (with no effect on the intended operation of these aspects).

In response to a submission, the allowed plasmids for exempt dealings involving *Agrobacterium* (as a host and as a vector in plant tissue culture systems) were reconsidered and updated so as to reflect the original intention of the clauses. This has the effect that Ri plasmids are only permitted if disarmed.

Changes with no impact on operation of the amendments

Minor changes to several amendment items were made to improve clarity without altering the intended operation of the amendments:

- The proprietary product names NoGall and Vaxsafe PM were removed from new items in the list of “organisms that are not GMOs”, leaving only strain names. This change was made in response to submitters commenting that inclusion of product names makes the applicability of the clauses to other products ambiguous, and that it is unusual to include product names in legislative instruments.
- A typographical error was corrected in an amendment to Schedule 2 Part 1 table item 4 subparagraph (2)(e), and the same clause altered to clarify the requirements for using viral sequences as donor nucleic acid in exempt dealings.
- The reference to the IBC that assesses an NLRD, in the list of information to be notified to the Regulator, was corrected.
- The wording to include null segregants in the list of “organisms that are not GMOs” (Schedule 1 item 8) was altered for improved clarity.

The name of the instrument and the responsible Minister were also updated.

Additions to facilitate transition to amended GT Regulations

Further consideration was given to commencement of amendment items relating to NLRD records of assessment and NLRD notifications to the Regulator. These items were moved to a new Schedule of the amendments which would commence on 1 July 2019, the start of the annual NLRD reporting period. As a result, these requirements will be consistent for all NLRDs assessed within the reporting period, rather than changing part-way through a reporting period.

Transitional provisions were added to enable short-term continuation of dealings for which authorisation requirements would be changed:

- Dealings that will no longer be exempt or NLRDs may continue to be conducted at the old authorisation level for up to 1 year, while authorisations are sought
- NLRDs for which facility requirements have changed may continue to be conducted in the same facilities for up to 1 year
- NLRDs assessed by an IBC prior to commencement of amendments may continue to be conducted according to all other NLRD requirements, even though IBCs must record a new field of information for newly assessed NLRDs.

Appendix D: Introduction to new technologies

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. 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 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.

Gene drives

Gene drives are genetic elements that are able to be inherited at a greater than expected rate. Most sexually reproducing organisms have two sets of genes, one from each parent. They then pass on half of their genes (a random mix from each parent) to their offspring. Gene drives are mechanisms that ensure that certain genetic elements are passed on to more than half of the offspring. In some cases gene drives may even be passed to all the offspring. This means that the genetic elements associated with the gene drives are able to increase in prevalence in a population at a faster rate than other genes.

Scientists have known about various naturally occurring gene drive mechanisms for decades, but it is only recently, with the development of CRISPR/cas9 and other site directed nucleases, that scientists have been able to build and test their own gene drives.

Initial experiments suggest that these GM gene drives work well in highly inbred laboratory populations of insects or mice. However, it has been suggested that these drives may be less effective in wild populations with greater genetic variability.

Internationally, there is rapidly growing research interest in using 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.

It should be noted that there are other types of genes and genetic mechanisms that may be able to become rapidly dominant within a population. For example, bacterial genes for antibiotic resistance rapidly become widespread when that antibiotic is present. Genes which are inherited in a sex specific manner, or which influence the sex ratio or reproductive capacity of offspring may also cause changes in the genepool at the population level. However, these are not gene drives.

RNA interference

RNAi, also known as gene silencing, is a group of natural cellular mechanisms in most higher organisms that reduce the production of specific proteins. RNAi relies on gene-specific small RNAs, processed from longer RNAs, which guide mechanisms to reduce the amount of protein produced from that gene. RNAi can take effect via degradation of the target gene's RNA transcript; repression of translation of the transcript into protein; methylation of the target gene; or a combination of these mechanisms.

RNAi is an important natural mechanism to regulate the level of each protein present in the cell, and RNAi also plays an important role in defence against viral infections. RNAi can also be utilised to silence the expression of a chosen target gene, permanently or temporarily.

Silencing a chosen target gene can be achieved by expression of target-specific RNAs that form a double-stranded structure (e.g. short or long hairpin RNAs). The double-stranded RNAs are processed by native enzymes into short interfering RNAs, which guide further RNAi enzymes to cause the silencing effect. To achieve stable silencing these RNAs are expressed from genomic insertions, delivered by standard gene technology techniques for introducing transgenes, or from vectors that propagate outside an organism's genome. The RNAi effect is inherited by offspring inheriting the genomic insertions or vectors.

Short-lived RNAi can be achieved through short-term expression of double-stranded RNAs, e.g. from introduced GM *Agrobacterium tumefaciens* that does not integrate sequences into the genome in plant cells, or using viral vectors. Other short-lived RNAi techniques, referred to in this document as RNA-delivered RNAi techniques, involve directly introducing double-stranded RNAs, short interfering RNAs or microRNAs into an organism. The silencing effect of short-lived RNAi techniques occurs while the triggering RNA is present, and may persist for variable periods afterwards due to genomic DNA methylation.