Overview of amendments to the Gene Technology Regulations 2001

This document has been prepared to assist regulated organisations to understand the Gene Technology Amendment (2019 Measures No. 1) Regulations 2019 (the Amendment Regulations).

Only the aspects of the Amendment Regulations that directly affect regulated organisations are described below. This document is not intended to be a comprehensive summary of all amendments nor does it provide legal advice. Refer to the Amendment Regulations itself for an authoritative statement of the law. Further information on all amendments is available in the Explanatory Statement. If you are unsure about how to meet your legal obligations, OGTR suggests you seek your own legal advice.

This document describes the following amendments:

Commencing **8 October 2019**:

- amendments clarifying the scope of regulation – what is a GMO (site-directed nuclease (SDN) techniques, oligonucleotide-directed mutagenesis (ODM), RNA interference, null segregants)
- minor amendments to Notifiable Low Risk Dealing (NLRD) requirements
- amendments to contained dealings classifications (exempt dealings, NLRDs and Dealings Not involving Intentional Release (DNIRs))

Commencing **1 July 2020**:

- minor amendments to Institutional Biosafety Committee (IBC) records of assessment for NLRDs
- minor amendments to NLRD reporting

Commencing **8 October 2020**:

- repeal of Schedule 1 item 1.

When each Schedule of the Amendment Regulations commences the official compilation of the Regulations on the Federal Register of Legislation will be updated. Future law compilations, which show how the amendments will change the Regulations in the future, are available on the OGTR website to assist regulated organisations to prepare for each part of the amendments commencing.

Until each phase of amendments commences, the previous version of the Gene Technology Regulations 2001 (the Regulations) remains in force and must be followed.

Amendments commencing 8 October 2019

Refer to future law compilation incorporating amendments from Schedule 1

Clarifying the scope of Regulation - What is a GMO

Organisms modified using SDN-1 are not GMOs

Schedule 1 lists organisms that are not GMOs for the purposes of the *Gene Technology Act 2000* (the Act). The amendments add items to this list to exclude organisms modified through unguided repair of site-directed nuclease activity, also known as SDN-1 organisms, from regulation as GMOs. Unguided repair means that no nucleic acid template was added to cells to guide genome repair following SDN application. SDNs include, but are not limited to, CRISPR/Cas9, zinc finger nucleases, meganucleases and TALENs.

Site-directed nucleases can be applied in a variety of ways to produce SDN-1 organisms. Some of these methods generate GMOs in intermediate steps, and dealings with these GMOs will continue to require authorisation under the Act. The table below summarises the status of organisms with SDN-1 modifications, provided that the organisms have no other modifications from gene technology beyond those described in the table.

<table>
<tr><td rowspan="2"></td><td colspan="3">Method of site-directed nuclease application</td></tr>
<tr><td>SDN Protein (with or without sgRNA)</td><td>SDN expressed from a transgene that is only transiently present in the organism</td><td>SDN expressed from transgene integrated in the genome</td></tr>
<tr><td rowspan="2">Status of the initial organism modified by SDN-1</td><td rowspan="2">Not a GMO
(Schedule 1 item 4)</td><td>GMO while transgene or its expressed products are present</td><td rowspan="2">GMO</td></tr>
<tr><td>Not a GMO when transgene and expressed products have degraded (Schedule 1 items 4+10)</td></tr>
<tr><td>Status of offspring inheriting the SDN-1 modification</td><td>Not a GMO
(Schedule 1 item 9(a))</td><td>Not a GMO
(Schedule 1 item 9(b))</td><td>GMO if SDN transgene also inherited

Not a GMO if no SDN transgene inherited (Schedule 1 item 9(b))</td></tr>
</table>

Some examples illustrating the status of organisms produced in the course of using SDN-1, under the amendments, are:

- An organism supplied with Cas9 protein and guide RNA/s in which an SDN-1 modification occurs is not a GMO.
- An organism expressing Cas9 and guide RNA/s from an expression cassette not integrated into the genome is a GMO while the expression cassette or its expressed products are present. If the expression cassette and its expressed products have degraded over time and only SDN-1 modifications remain, the organism is not a GMO.
- An organism with Cas9 and guide RNA transgenes integrated into its genome is a GMO, but those of its segregating offspring carrying an SDN-1 modification but lacking the Cas9 and gRNA transgenes are not GMOs.

In each example, this status depends upon:

- no nucleic acid template being supplied to guide genome repair through homology-directed recombination, and
- the organism having no other modifications as a result of gene technology.

It is the responsibility of proponents to comply with the law and ensure that these requirements have been met.

SDN-1 organisms may be subject to regulation by other agencies, depending upon their characteristics and intended uses.

This amendment does not exclude organisms modified using base editing methods from regulation as GMOs, because the amendment is specific to enzymes with nuclease activity. Base editing methods use disabled CRISPR/Cas9 coupled with other enzymatic domains to modify genes or genetic material, e.g. cytidine deaminase or adenosine deaminase.

Organisms modified using template-guided SDN techniques and ODM are GMOs

New Schedule 1B, Organisms that are genetically modified organisms, operating via new Regulation 4A, provides that:

- organisms modified using oligonucleotide-directed mutagenesis are GMOs (**Schedule 1B item 1**)
- organisms modified using SDN techniques involving templates to guide repair of SDN action, also known as SDN-2 and SDN-3, are GMOs (**Schedule 1B item 2**).

In each case, the method used to modify the organism is central to determining whether or not the organism is a GMO. The number of resulting nucleotide changes, whether insertions or deletions, or whether the resulting nucleotide sequence may be found in sexually compatible species, is not a deciding factor.

Some RNA interference (RNAi) techniques are not gene technology

The amendments list RNAi techniques involving directly applying RNAs to temporarily induce RNAi, as a technique that is not gene technology in **item 11 of Schedule 1A**. As a result, organisms modified using these techniques will not be classified as GMOs.

The RNAs could be introduced to the organism by any method including, but not limited to:

- the organism taking up an externally applied RNA (e.g. by spraying with or dipping in an RNA solution)
- injecting RNA into the organism
- electroporation, and
- methods leading to the organism consuming material to which the RNA has been applied (e.g. insects consuming RNA by feeding on plant material sprayed with RNA).

To ensure that only short-lived RNAi techniques are excluded, this exclusion only applies if:

- the organism's genomic DNA sequence cannot be changed by the technique (this requirement can be met even if changes to genomic DNA methylation can occur), and
- the introduced RNA cannot be translated into a protein or lead to the production of infectious agents.

Provided the above requirements are met, the applied RNAs could potentially include small interfering RNAs, artificial microRNAs, short or long double-stranded RNAs and hairpin RNAs, with sequence of any origin. It is the responsibility of proponents to comply with the law and ensure that the requirements above have been met.

This amendment does not change the status of organisms to which other RNAi techniques have been applied, e.g. where an organism is stably or transiently transformed with a transgene able to express RNA that can induce gene silencing, this remains a GMO.

This amendment does 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.

Organisms derived from GMOs but with no traits from gene technology

This amendment will clarify the non-GMO status of organisms derived from GMOs but which do not possess traits as a result of gene technology. The purpose of this amendment is to provide clarity for the avoidance of doubt, and it does not change the status of any organisms. These organisms are:

- offspring of GMOs that have not inherited traits that occurred in a parent because of gene technology, commonly referred to as null segregants (**Schedule 1 item 8**)
- organisms temporarily modified using gene technology but which have lost all traits (e.g. transgenes, products expressed from transgenes) that occurred because of gene technology (**Schedule 1 item 10**).

Modifications produced using SDN techniques are traits that occurred because of gene technology, so item 8 does not exclude these organisms from being GMOs. However, other items described above do exclude SDN-1 organisms from regulation.

Minor clarifications to NLRD requirements

NLRD time limit

When a five year time limit for NLRDs was introduced in 2011, transitional provisions were put in place for previously assessed NLRDs (regulation 13A). These provisions have now ceased to have effect, and will be repealed. The amendments will provide a uniform five year time limit for NLRDs in paragraph **13(1)(d)**. The duration of existing and future NLRDs is unchanged by this amendment.

NLRD facilities, and GMO transportation storage and disposal

The amendments clarify, but do not change, the facilities in which a NLRD may be undertaken. Paragraph **13(1)(f)** specifies that NLRDs can only be undertaken in facilities mentioned in the IBC's record of assessment as appropriate for the dealing. The amendments additionally limit the facilities in which a NLRD may be undertaken to facilities described in subregulation **13(2)**, i.e. facilities certified to at least PC2 for NLRDs listed in Schedule 3, clause 2.1, or certified to least PC3 for NLRDs listed in Schedule 3, clause 2.2. In all cases, facilities must be appropriate for the dealing, e.g. plant facilities for dealings with GM plants. This replaces a reference in paragraph 13(1)(i), which is repealed. Subregulation **13(3)** continues to provide requirements for transportation, storage or disposal of GMOs outside permitted facilities, and is also adjusted accordingly.

Categorisation of contained dealings

Transitional arrangements

Regulation 41 provides transitional arrangements for dealings currently being conducted as exempt dealings or NLRDs but which require a higher level of authorisation as a result of the amendments, or where the requirements for undertaking a NLRD change (e.g. the required containment level increases). A person conducting such a dealing will have one year in which they can continue the dealing under the pre-existing authorisation, and after that time they must either cease the dealing or have obtained a suitable authorisation.

Dealings with genes drive GMOs require a licence

Contained dealings with GMOs containing functional gene drives, i.e. genetic modifications that enhance the inheritance of particular traits in sexually reproducing organisms, will require a DNIR licence (**Schedule 3 3.1(r)**). Dealings with viral vectors that can modify an organism to produce an engineered gene drive will also require a DNIR licence (**Schedule 3 3.1(s)**).

OGTR's assessment of applications will ensure case-by-case evaluation of risks and tailored risk management of activities with these organisms. Case-by-case evaluation will take into account any risk-mitigating effects of molecular, environmental or physical containment approaches proposed in each case (e.g. split drives, daisy drives, synthetic targets, etc.).

Organisations affected by this amendment should familiarise themselves with the information requirements for licence applications and allow time for preparation and assessment of a licence application before the end of the transitional period. The Regulator must make a decision on DNIR licence applications within 90 working days (approximately four calendar months) of receiving a complete application.

Cloned viral genomes in exempt dealings

Dealings with cloned viral sequences are classified in the Regulations as exempt dealings only if at least one viral gene essential for viral multiplication is missing. **Schedule 2, Part 1, item 4(2)** will additionally list as exempt, dealings involving cloned full length viral genomes that are unable to produce infectious agents in any potential host species without additional non-host genes or gene products that will not be available during the dealing.

Dealings with cloned viral genomes that are able to give rise to infectious agents when introduced into a host cell will continue to be regulated as if they were dealings with the virus itself.

New exempt hosts

The amendments add two host species to the list of host/vector systems for exempt dealings in **Schedule 2 part 2 (item 6)**:

- *Zymomonas mobilis* and
- *Corynebacterium glutamicum.*

The amendments also update Schedule 2 part 2 to current legislative drafting requirements, including changes to table item numbering to improve clarity.

Viral vectors with no host

The amendments will improve clarity about the classification of dealings with virions with no host by classifying these dealings at the same level as dealings involving the introduction of these vectors into listed exempt hosts. This will take effect through a new definition of 'host/vector system' and an amended definition of 'non-vector system' in **regulation 3**, and new wording in **Schedule 2, part 2, 2.1, Schedule 3, 1.1(c), 2.1 (d),** and **(i-m)** and **3.1(1)(d)**. This also applies to viral vectors listed as part of exempt dealings and which themselves meet the definition of organisms in the Act (being virions of replication defective viral vectors unable to transduce human cells, specified GM baculovirus genomes or virions, and specified GM bacteriophage genomes or virions).

Clarifying requirements for characterisation of modifications

The amendments will change the wording around pathogenic determinants and introduced DNA to shift the focus of the categorisation of dealings towards the outcome of the modification (e.g. immunomodulatory effects, ability to cause harm) rather than the characteristics of the introduced sequences. This will take effect through an amended definition of 'characterised' in **regulation 3**, and new wording in **Schedule 3, 1.1(c), 2.1(d), (e), (k) and (m)** and **3.1(1)(d)-(f)**. This will ensure the appropriate classification of dealings involving modifications other than the introduction of DNA, such as deletions and small changes in nucleotide sequence. This will avoid dealings being classified at a lower level than is appropriate for the risks they may pose. For example, for Schedule 3, 1.1(c), 2.1(k) and 3,1(d) & (e), an introduced sequence may not encode a protein with immunomodulatory activity but nonetheless have an immunodulatory effect, such as by silencing a gene involved in immune regulation.

Clarification of risk group considerations

The previous review of the Regulations in 2011 introduced a new category of NLRD for dealings with risk group 3 microorganisms and required a licence for all dealings with risk group 4 microorganisms. Additional amendments (**Schedule 3, 2.2 (2) & (3)** and **3.1(1)(q), (2)-(4)**) now clarify that when applying these provisions, the relevant risk group is that of the unmodified parent organism. Any

effect of the modification on risk grouping (e.g. loss of virulence or host range) is not a factor IBCs can consider when assessing the appropriate category for dealings with these GMO.

Amendments commencing 1 July 2020

Refer to future law compilation incorporating amendments from Schedule 2

Minor amendments to the requirements for IBC records of NLRD assessment and NLRD notification to the Regulator are intended to clarify current requirements without substantially changing them. Organisations would be able to meet these changed requirements simply by using the latest NLRD reporting form and record of assessment guidance documents provided by OGTR.

IBC Records of Assessment of NLRDs

The amendments will require that in assessing the kind of dealing a proposed NLRD is, IBCs must record not only the kind of dealing as mentioned in Part 1 or 2 of Schedule 3, but also whether or not the dealing is mentioned in Part 3 of Schedule 3 (subparagraphs **13B(a)(iii) and (iv)**). This will ensure that IBCs assessing whether a proposed dealing is a NLRD take into account that dealings listed in Schedule 3 Part 3 (dealings that are not NLRDs) are not NLRDs even if they are also listed in the NLRD categories provided in parts 1 and 2. For example, some dealings involving expression of toxins may be consistent with some NLRD categories but are prevented from classification as NLRDs through Schedule 3 Part 3 3.1(a) or (b). This amendment does not change the authorisation category of any dealings.

In assessing what facilities are appropriate for a proposed NLRD, the amendments require IBCs to have regard to the facility requirements described in subregulation 13(2) (subparagraph **13B(a)(vii)**). Subregulation 13(2) allows that NLRDs may be undertaken in facilities certified to at least PC2 for NLRDs listed in Schedule 3, clause 2.1, or certified to least PC3 for NLRDs listed in Schedule 3, clause 2.2. In all cases, facilities must be appropriate for the dealing, e.g. plant facilities for dealings with GM plants. This amendment makes clearer, but does not change, the range of facilities an IBC may consider.

NLRD provisions – language adjustments

The amendments make several small adjustments to language in regulations 13B and 39, for clarity and consistency with the *Gene Technology Act 2000*. These amendments include:

- referring to a 'person or persons' who proposes to undertake NLRDs, instead of current references to organisations or accredited organisations (subparagraph **13B(a)(x)** for IBC records of assessment, paragraph **39(a)** for NLRD notifications to the Regulator). Importantly, the *Acts Interpretation Act 1901* provides that the term 'person' in legislation includes "a body politic or corporate as well as an individual". Unless only applicable to one person, it is not intended that individuals be named for NLRD reporting purposes; the name of a company (or other legal entity) that has oversight of the individuals undertaking the dealings will meet the requirement.
- distinguishing between persons that submitted a NLRD proposal and persons that would undertake the dealing (subparagraph **13B(a)(i)** for IBC records of assessment, paragraph **39(c)** for NLRD notifications to the Regulator).

These language adjustments do not change the underlying matters to be addressed between NLRD proponents, IBCs and accredited organisations. The adjustments would not necessarily have any practical change to the way organisations/entities submit the proposal to an IBC, undertake dealings or notify the Regulator.

Annual NLRD reporting

The unamended Regulations require that all dealings assessed by IBCs to be NLRDs are notified to the Regulator annually. The amendments will require this reporting be completed by 30 September of the financial year following the one in which the assessment was made (paragraph **13C(2A)**). This will align the reporting timeframes for NLRDs submitted by both accredited and non-accredited organisations.

Transitional arrangements

Amended paragraph 13B(a)(iii) requires IBCs to record their assessment that a proposed dealing is not mentioned in Part 3 of Schedule 3 (dealings that are not NLRDs). However, NLRDs assessed prior to commencement of these amendments would not necessarily record this. **Regulation 42** makes clear that NLRDs assessed prior to commencement of the requirement can continue to be undertaken, even if IBC assessment did not record an assessment that a proposed dealing is not mentioned in Part 3 of Schedule 3.

Regulation 43 provides that NLRDs assessed by an IBC to be NLRDs between 1 July 2019 and 30 June 2020 must be reported to the Regulator in accordance with the amended regulation 13C i.e. reporting the updated fields of information listed in amended subregulation 13C(2) to the Regulator between 1 July 2020 and 30 September 2020.

Amendment commencing 8 October 2020

Repealing Schedule 1 item 1

Item 1 of Schedule 1 will be repealed to improve clarity about which organisms are regulated as GMOs. When this item was first listed in 2001 it excluded organisms modified using chemical and radiation-induced mutagenesis from GMO regulation. However, since that time these techniques have been listed as techniques that are not gene technology in Schedule 1A (items 2-4). As a result, the non-GMO status of organisms mutagenised with chemicals and radiation is unchanged by the repeal of item 1 of Schedule 1.

The non-GMO status of two organisms known to be excluded from regulation through item 1, NoGall and VaxSafe PM, will be maintained by their listing in new **items 11** and **12** of Schedule 1 under their strain names.